

SUPPLEMENTARY TABLES AND FIGURES

sTable 1	ICD-9 codes for major congenital malformations	3
sTable 2	ICD-9 and CPT codes for preterm delivery	4
sTable 3	Covariates included in each of the analyses and the associated covariate assessment window	5
sTable 4	Cohort characteristics of pregnancies with exposure to duloxetine versus no exposure to duloxetine during the first trimester	6
sTable 5	Cohort characteristics of pregnancies with exposure to duloxetine versus exposure to SSRIs during the first trimester	10
sTable 6	Cohort characteristics of pregnancies with exposure to duloxetine versus exposure to venlafaxine during the first trimester	14
sTable 7	Cohort characteristics of pregnancies with exposure to duloxetine during the first trimester versus duloxetine discontinuers (i.e., exposure before but not during the first trimester)	18
sFigure 1	Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses	22
sFigure 2	Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses	23
sFigure 3	Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification	24
sFigure 4	Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses	25
sFigure 5	Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification	26
sFigure 6	Risk of preterm birth associated with <u>early</u> exposure to duloxetine: sensitivity analyses	27
sFigure 7	Risk of preterm birth associated with <u>early</u> exposure to duloxetine: sensitivity analyses to address outcome misclassification	28
sFigure 8	Risk of preterm birth associated with <u>late</u> exposure to duloxetine: sensitivity analyses	29
sFigure 9	Risk of preterm birth associated with <u>late</u> exposure to duloxetine: sensitivity analyses to address outcome misclassification	30

sFigure 10	Risk of small for gestational age associated with <u>early</u> pregnancy exposure to duloxetine: sensitivity analyses	31
sFigure 11	Risk of small for gestational age associated with <u>early</u> pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	32
sFigure 12	Risk of small for gestational age associated with <u>late</u> pregnancy exposure to duloxetine: sensitivity analyses	33
sFigure 13	Risk of small for gestational age associated with <u>late</u> pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification	34
sFigure 14	Risk of preeclampsia associated with <u>early</u> exposure to duloxetine: sensitivity analyses	35
sFigure 15	Risk of preeclampsia associated with <u>early</u> exposure to duloxetine: sensitivity analyses to address outcome misclassification	36
sFigure 16	Risk of preeclampsia associated with <u>late</u> exposure to duloxetine: sensitivity analyses	37
sFigure 17	Risk of preeclampsia associated with <u>late</u> exposure to duloxetine: sensitivity analyses to address outcome misclassification	38
sFigure 18	Risk of postpartum hemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses	39
sFigure 19	Risk of postpartum hemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification	40
sFigure 20	External adjustment of the observed relative risk for any malformation to account for confounding by obesity, smoking, and alcohol using NHANES	41
sFigure 21	External adjustment of the observed relative risk for cardiac malformations to account for confounding by obesity, smoking, and alcohol using NHANES	42
sFigure 22	External adjustment of the observed relative risk for preterm/SGA to account for confounding by obesity, smoking, and alcohol using NHANES	43
sFigure 23	External adjustment of the observed relative risk for preeclampsia to account for confounding by obesity, smoking, and alcohol using NHANES	45
sFigure 24	External adjustment of the observed relative risk for postpartum haemorrhage to account for confounding by obesity, smoking, and alcohol using NHANES	46

For any additional results, please refer to the full report for study EUPAS 15946, which is available for download at
<http://www.encepp.eu/encepp/openAttachment/fullProtocol/16045>.

sTable 1 ICD-9 codes for major congenital malformations

Malformation Group	ICD-9 Code*
1. Central Nervous System	740.xx-742.xx
2. Eye Anomalies	743.xx (exclude if only 743.6x and 743.8x)
3. Ear Anomalies	744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)
4. Cardiovascular malformations	745.xx-747.xx (exclude if only 745.5 AND preterm, 746.02 AND preterm, 746.4x, 746.6x, 746.99, 747.0x and preterm, 747.3 and preterm, 747.5x)
5. Other vascular (non-cardiac)	747.6x-747.9x (exclude if only 747.83)
6. Respiratory malformations	748.xx (do not count if only 748.1x)
7. Oral cleft	749.xx
8. Gastrointestinal	750.xx-751.xx (do not count if only 750.0x, 750.1x, 750.50, 751.0x)
9. Genital (male and female)	752.xx-753.xx (do not count if only 752.42, 752.52) (in addition, do not count 752.5x if preterm)
10. Urinary	753.xx (do not include if only 753.7x)
11. Musculoskeletal (no limbs, includes omphalocele ad gastroschisis)	754.xx and 756.xx (do not count if only 754.3x, 754.81, 754.82, 756.2x)
12. Limb defects	755.xx (exclude if only 755.65)
13. Other	757.xx; 759.xx (excl if only 757.2-757.6, 759.81-759.83)
Major malformation overall	Any of the 13 specific malformation groups present

* Malformation was considered present if:

- >1 date with an ICD-9 code indicating a malformation or,
- 1 date with an ICD-9 code indicating a malformation and a specific surgery code for the correction of a malformation, or
- 1 date with an ICD-9 code indicating a malformation and infant death in the first 30 days.

If there was a code for the malformation group in the maternal records between 90 days prior to the LMP and LMP+105 and there were no codes in the infant record between delivery and delivery+90 (i.e., the outcome was defined based on maternal codes between delivery and delivery+30), then the malformation was considered maternal and the infant was considered unaffected.

sTable 2 ICD-9 and CPT codes for preterm delivery

ICD-9	Description
644.2x	early onset of delivery
776.6x	anemia of prematurity
362.20	retinopathy of prematurity, unspecified
362.22	retinopathy of prematurity, stage 0
362.23	retinopathy of prematurity, stage 1
362.24	retinopathy of prematurity, stage 2
362.25	retinopathy of prematurity, stage 3
362.26	retinopathy of prematurity, stage 4
362.27	retinopathy of prematurity, stage 5
765.xx, excluding 765.09, 765.19, 765.20, 765.29	disorders relating to short gestation and low birth-weight
CPT	
49491	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
49492	repair, initial inguinal hernia, preterm infant (younger than 37 weeks gestation at birth), performed from birth up to 50 weeks postconception
67229	treatment of extensive or progressive retinopathy, 1 or more sessions; preterm infant (less than 37 weeks gestation at birth), performed from
00836	anesthesia for hernia repairs in the lower abdomen not otherwise specified, infants younger than 37 weeks gestational age at birth

sTable 3 Covariates included in each of the analyses and the associated covariate assessment window

Covariate assessment window			
Congenital malformations	Postpartum hemorrhage	Preterm, Small for gestational age, preeclampsia	
		Early exposure	Late exposure
Maternal demographics characteristics			
Age, Race/ethnicity, Geographic region			
n/a	n/a	n/a	n/a
Indications for duloxetine			
Depression, Anxiety, Neuropathic Pain, Fibromyalgia, Non-neuropathic Pain			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
Comorbid medical conditions			
<ul style="list-style-type: none"> Chronic hypertension, Diabetes, Renal Disease, Obesity or overweight, Obstetric comorbidity score (divided into quartiles) Other psychiatric conditions (Sleep disorder, Bipolar disorder, Psychosis, Schizophrenia, Personality disorder, Adjustment disorder) Tobacco use, alcohol abuse or dependence, drug abuse or dependence 			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<ul style="list-style-type: none"> Infections (Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Syphilis, Varicella, Parvovirus B19, Zika virus, Lymphocytic choriomeningitis virus (LCMV), Influenza, chlamydia, human papilloma virus, gonorrhea, HIV, trichomoniasis) 			
3 months pre-LMP to 90 days after LMP	n/a	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
Obstetrical conditions			
Multifetal gestation			
LMP to delivery	LMP to delivery	LMP to delivery	LMP to delivery
Maternal medications			
<ul style="list-style-type: none"> Benzodiazepines, Other hypnotics, Barbiturates, Anxiolytics, Anticonvulsants, Antipsychotics, Antidepressants (other than duloxetine), Stimulants, Antidiabetic oral medications, Insulin, Antihypertensive, Opioid analgesics, Triptans, NSAIDs 			
3 months pre-LMP to 90 days after LMP	4 months prior to delivery to 1 day prior to delivery	3 months pre-LMP to 140 days after the LMP	3 months pre-LMP to 245 days after the LMP
<ul style="list-style-type: none"> Potentially teratogenic medication exposures (ACEI, Danazol, Progestins, Methimazole, Propylthiouracil, Corticosteroids, Fluconazole) ⁽¹⁾ 			
Days supply overlapping T1	n/a	n/a	n/a
Measures of healthcare utilization			
Number of non-duloxetine generics, Number of outpatient medical visits, Number of hospital admissions, Number of distinct 3 digit ICD 9 codes, Number of emergency department, Psychiatric hospitalization, Visits with a psychiatrist			
3 months pre-LMP to LMP	4 months prior to delivery to 1 month prior to delivery	3 months pre-LMP to LMP	3 months pre-LMP to 140 days after the LMP

(1) Pregnant women with exposure to known teratogens (i.e., warfarin, antineoplastic agents, lithium, isotretinoin, misoprostol, thalidomide) were excluded from the cohort, whereas those with exposure to suspected teratogens were included. Suspected teratogens were included as covariates in the propensity score model.

sTable 4 Cohort characteristics of pregnancies with exposure to duloxetine versus no exposure to duloxetine during the first trimester

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Unexposed		Stand Diff ⁽¹⁾	Duloxetine		Unexposed		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Total	2,532	100.00	1,284,827	100.00		2,223	100.00	392,928	100.00	
Age, mean (SD)	27.74	5.53	24.934	5.36	0.51	27.81	5.55	27.76	5.56	0.01
Race, N (%)										
White	2,003	79.11	518,455	40.35	0.86	1,761	79.22	315,827	80.38	-0.03
Black or African American	219	8.65	400,432	31.17	-0.59	193	8.68	30,859	7.85	0.03
Hispanic or Latino	70	2.76	181,970	14.16	-0.42	61	2.74	9,549	2.43	0.02
Asian or Other Pacific Islander	32	1.26	56,128	4.37	-0.19	30	1.35	5,155	1.31	0.00
American Indian	33	1.30	21,136	1.65	-0.03	29	1.30	5,056	1.29	0.00
Other	117	4.62	75,858	5.90	-0.06	101	4.54	18,013	4.58	0.00
Unknown	58	2.29	30,848	2.40	-0.01	48	2.16	8,469	2.16	0.00
Chronic comorbid conditions, N (%)										
Hypertension	191	7.54	34,556	2.69	0.22	173	7.78	30,313	7.71	0.00
Diabetes	152	6.00	30,063	2.34	0.18	135	6.07	23,922	6.09	0.00
Renal Disease	23	0.91	4,695	0.37	0.07	22	0.99	3,970	1.01	0.00
Obesity Overweight	152	6.00	33,501	2.61	0.17	142	6.39	24,906	6.34	0.00
Infections, N (%)										
Toxoplasmosis	0	0.00	168	0.01	-0.02	0	0.00	0	0.00	
Rubella	0	0.00	146	0.01	-0.02	0	0.00	0	0.00	
Cytomegalovirus	0	0.00	46	0.00	-0.01	0	0.00	0	0.00	
Herpes	41	1.62	10,470	0.81	0.07	35	1.57	6,382	1.62	0.00
Syphilis	0	0.00	1,112	0.09	-0.04	0	0.00	0	0.00	
Varicella	<11	0.04	236	0.02	0.01	0	0.00	0	0.00	
Parvovirus B19	0	0.00	31	0.00	-0.01	0	0.00	0	0.00	

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Unexposed		Stand Diff ⁽¹⁾	Duloxetine		Unexposed		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Zika virus other mosquito	0	0.00	0	0.00	0.00	0	0.00	0	0.00	
Lymphocytic choriomeningitis	<11	0.04	12	0.00	0.03	0	0.00	19	0.00	-0.01
Influenza	21	0.83	8,263	0.64	0.02	19	0.85	3,297	0.84	0.00
Chlamydia	11	0.43	8,447	0.66	-0.03	<11	0.45	1,841	0.47	0.00
Human papilloma virus	25	0.99	6,735	0.52	0.05	22	0.99	3,857	0.98	0.00
Gonorrhea	13	0.51	9,783	0.76	-0.03	<11	0.45	1,725	0.44	0.00
HIV	<11	0.28	3,911	0.30	-0.01	<11	0.27	1,030	0.26	0.00
Trichomoniasis	18	0.71	16,337	1.27	-0.06	16	0.72	2,702	0.69	0.00
Indications for duloxetine, N (%)										
Depression	1,235	48.78	77,678	6.05	1.09	1,234	55.51	223,353	56.84	-0.03
Anxiety	778	30.73	52,167	4.06	0.75	777	34.95	138,909	35.35	-0.01
Neuropathic Pain	267	10.55	20,024	1.56	0.38	267	12.01	46,252	11.77	0.01
Fibromyalgia	264	10.43	11,829	0.92	0.42	263	11.83	42,201	10.74	0.03
Non neuropathic Pain	1,234	48.74	198,581	15.46	0.76	1,233	55.47	213,645	54.37	0.02
Other psychiatric conditions, N (%)										
Sleep disorder	144	5.69	10,560	0.82	0.28	136	6.12	23,672	6.02	0.00
Bipolar disorder	330	13.03	17,340	1.35	0.46	294	13.23	50,799	12.93	0.01
Psychosis	20	0.79	2,570	0.20	0.08	19	0.85	3,359	0.85	0.00
Schizophrenia	25	0.99	2,096	0.16	0.11	23	1.03	4,041	1.03	0.00
Personality disorder	56	2.21	2,613	0.20	0.18	55	2.47	9,490	2.42	0.00
Adjustment disorder	29	1.15	4,620	0.36	0.09	25	1.12	4,382	1.12	0.00
Tobacco use, N (%)	279	11.02	52,341	4.07	0.27	266	11.97	47,559	12.10	0.00
Alcohol abuse or dependence, N (%)	31	1.22	4,744	0.37	0.10	28	1.26	5,054	1.29	0.00
Drug abuse or dependence, N (%)	84	3.32	11,587	0.90	0.17	80	3.60	14,339	3.65	0.00

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Unexposed		Stand Diff ⁽¹⁾	Duloxetine		Unexposed		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Other medication exposures, N (%)										
Benzodiazepines	979	38.67	46,726	3.64	0.95	911	40.98	160,239	40.78	0.00
Other hypnotics	608	24.01	48,070	3.74	0.61	563	25.33	97,232	24.75	0.01
Barbiturates	124	4.90	14,042	1.09	0.22	111	4.99	19,572	4.98	0.00
Anxiolytics	129	5.09	5,852	0.46	0.29	118	5.31	20,392	5.19	0.01
Anticonvulsants	642	25.36	29,354	2.28	0.71	590	26.54	99,450	25.31	0.03
Antipsychotics	505	19.94	18,630	1.45	0.63	463	20.83	77,907	19.83	0.02
SSRIs	705	27.84	88,971	6.92	0.57	645	29.01	121,358	30.89	-0.04
SNRIs	103	4.07	10,809	0.84	0.21	92	4.14	17,233	4.39	-0.01
Other Antidep	720	28.44	40,109	3.12	0.74	667	30.00	116,681	29.70	0.01
Stimulants	198	7.82	10,738	0.84	0.35	172	7.74	29,167	7.42	0.01
Antidiabetic	100	3.95	13,468	1.05	0.19	86	3.87	15,036	3.83	0.00
Insulin	80	3.16	12,212	0.95	0.16	69	3.10	12,322	3.14	0.00
Antihypertensives	373	14.73	41,000	3.19	0.41	329	14.80	56,095	14.28	0.01
Opioid analgesics	1,554	61.37	310,792	24.19	0.81	1,425	64.10	252,815	64.34	0.00
Triptans	178	7.03	15,504	1.21	0.30	165	7.42	28,900	7.36	0.00
NSAIDs	958	37.84	221,631	17.25	0.47	894	40.22	157,677	40.13	0.00
Obstetric conditions, N (%)										
Multifetal gestation Flag	87	3.44	47,282	3.68	-0.01	77	3.46	13,572	3.45	0.00
Potentially teratogenic medication exposures, N (%)										
Danazol	0	0.00	21	0.00	-0.01	0	0.00	0	0.00	
Synthetic progestins	88	3.48	25,715	2.00	0.09	80	3.60	14,054	3.58	0.00
Methimazole	<11	0.12	678	0.05	0.02	<11	0.13	570	0.15	0.00
Propylthiouracil	<11	0.16	1,466	0.11	0.01	<11	0.18	742	0.19	0.00

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Unexposed		Stand Diff ⁽¹⁾	Duloxetine		Unexposed		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Corticosteroids	453	17.89	92,250	7.18	0.33	402	18.08	70,912	18.05	0.00
Fluconazole	133	5.25	28,109	2.19	0.16	115	5.17	19,664	5.00	0.01
Healthcare Utilization, mean (SD)										
Comorbidity Index	1.58	1.85	0.917	1.40	0.40	1.62	1.88	1.61	1.85	0.01
Morphine equivalents	19774	489396	754	67877	0.05	21635	521363	18278	373453	0.01
Number of diagnoses	5.95	4.65	2.799	3.33	0.78	6.33	4.70	6.43	4.77	-0.02
Number of ED visits	0.72	1.30	0.345	0.89	0.33	0.77	1.32	0.81	1.66	-0.03
Number of generics dispensed	5.63	4.19	1.807	2.48	1.11	5.88	4.25	5.93	4.31	-0.01
Number of hospitalizations	0.05	0.27	0.042	0.23	0.05	0.06	0.28	0.06	0.28	0.01
Number of outpatient visits	5.58	6.43	2.114	3.43	0.67	5.96	6.62	5.94	6.38	0.00
Number of psychiatric hospitalizations	0.04	0.22	0.006	0.09	0.17	0.04	0.23	0.04	0.23	0.01
Number of psychiatrist visits	2.28	4.94	0.326	2.14	0.51	2.48	5.09	2.46	5.05	0.00

(1) The standardized difference is estimated as $\frac{\bar{X}_{exp} - \bar{X}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$, where s^2 represents the sample variance in the duloxetine exposed and the reference group.

sTable 5 Cohort characteristics of pregnancies with exposure to duloxetine versus exposure to SSRIs during the first trimester

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		SSRI		Stand Diff ⁽¹⁾	Duloxetine		SSRI		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Total	1,966	100	52,018	100		1,703	100	39,395	100	
Age, mean (SD)	27.7	5.51	26.21	5.4	0.27	27.77	5.53	27.77	5.58	0
Race, N (%)										
White	1,547	78.69	38,077	73.2	0.13	1,344	78.92	31,110	78.97	0
Black or African American	179	9.1	6,131	11.79	-0.09	156	9.16	3,588	9.11	0
Hispanic or Latino	54	2.75	3,386	6.51	-0.18	46	2.7	1,041	2.64	0
Asian or Other Pacific Islander	24	1.22	556	1.07	0.01	22	1.29	514	1.3	0
American Indian	28	1.42	806	1.55	-0.01	25	1.47	574	1.46	0
Other	92	4.68	1,884	3.62	0.05	77	4.52	1,791	4.55	0
Unknown	42	2.14	1,178	2.26	-0.01	33	1.94	779	1.98	0
Chronic comorbid conditions, N (%)										
Hypertension	146	7.43	2,792	5.37	0.08	133	7.81	3,117	7.91	0
Diabetes	125	6.36	2,163	4.16	0.1	110	6.46	2,600	6.6	-0.01
Renal Disease	15	0.76	326	0.63	0.02	15	0.88	343	0.87	0
Obesity Overweight	124	6.31	2,209	4.25	0.09	115	6.75	2,667	6.77	0
Infections, N (%)										
Toxoplasmosis	0	0	<11	0.02	-0.02	0	0	0	0	
Rubella	0	0	<11	0.01	-0.01	0	0	0	0	
Cytomegalovirus	0	0	0	0	-0.01	0	0	0	0	
Herpes	32	1.63	680	1.31	0.03	27	1.59	637	1.62	0
Syphilis	<11	0	40	0.08	-0.04	0	0	0	0	
Varicella	<11	0.05	<11	0.02	0.02	0	0	0	0	
Parvovirus B19	0	0	0	0	-0.01	0	0	0	0	

	Unadjusted						Accounting for Propensity Score Strata					
	Duloxetine		SSRI		Stand Diff ⁽¹⁾	Duloxetine		SSRI		Stand Diff ⁽¹⁾		
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD			
Zika virus other mosquito	0	0	0	0	.	0	0	0	0			
Lymphocytic choriomeningitis	<11	0.05	0	0	0.03	0	0	0	0			
Influenza	15	0.76	517	0.99	-0.02	13	0.76	284	0.72	0		
Chlamydia	<11	0.51	248	0.48	0	<11	0.53	219	0.55	0		
Human papilloma virus	15	0.76	393	0.76	0	12	0.7	277	0.7	0		
Gonorrhea	<11	0.51	264	0.51	0	<11	0.41	163	0.41	0		
HIV	<11	0.25	206	0.4	-0.02	<11	0.23	90	0.23	0		
Trichomoniasis	16	0.81	496	0.95	-0.01	14	0.82	312	0.79	0		
Indications for duloxetine, N (%)												
Depression	904	45.98	22,382	43.03	0.06	902	52.97	20,951	53.18	0		
Anxiety	562	28.59	13,740	26.41	0.05	561	32.94	13,130	33.33	-0.01		
Neuropathic Pain	202	10.27	2,310	4.44	0.22	201	11.8	4,557	11.57	0.01		
Fibromyalgia	203	10.33	1,325	2.55	0.32	201	11.8	4,309	10.94	0.03		
Non neuropathic Pain	966	49.14	16,406	31.54	0.36	964	56.61	22,278	56.55	0		
Other psychiatric conditions, N (%)												
Sleep disorder	112	5.7	2,180	4.19	0.07	107	6.28	2,460	6.24	0		
Bipolar disorder	245	12.46	4,224	8.12	0.14	216	12.68	5,074	12.88	-0.01		
Psychosis	13	0.66	538	1.03	-0.04	12	0.7	278	0.71	0		
Schizophrenia	18	0.92	528	1.02	-0.01	16	0.94	377	0.96	0		
Personality disorder	30	1.53	712	1.37	0.01	29	1.7	689	1.75	0		
Adjustment disorder	19	0.97	602	1.16	-0.02	16	0.94	353	0.9	0		
Tobacco use, N (%)	213	10.83	4,565	8.78	0.07	200	11.74	4,674	11.86	0		
Alcohol abuse or dependence, N (%)	18	0.92	787	1.51	-0.05	15	0.88	341	0.87	0		
Drug abuse or dependence, N (%)	59	3	1,601	3.08	0	56	3.29	1,299	3.3	0		

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		SSRI		Stand Diff ⁽¹⁾	Duloxetine		SSRI		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Other medication exposures, N (%)										
Benzodiazepines	733	37.28	12,568	24.16	0.29	675	39.64	15,763	40.01	-0.01
Other hypnotics	441	22.43	7,593	14.6	0.2	402	23.61	9,366	23.77	0
Barbiturates	95	4.83	1,626	3.13	0.09	83	4.87	1,901	4.83	0
Anxiolytics	88	4.48	1,804	3.47	0.05	78	4.58	1,836	4.66	0
Anticonvulsants	496	25.23	5,950	11.44	0.36	451	26.48	10,297	26.14	0.01
Antipsychotics	373	18.97	6,081	11.69	0.2	337	19.79	7,897	20.05	-0.01
SSRIs	139	7.07	52,018	100	-5.13	125	7.34	39,395	100	-5.02
SNRIs	73	3.71	1,651	3.17	0.03	62	3.64	1,459	3.7	0
Other Antidep	532	27.06	9,636	18.52	0.2	492	28.89	11,355	28.82	0
Stimulants	161	8.19	2,376	4.57	0.15	139	8.16	3,164	8.03	0
Antidiabetic	80	4.07	1,276	2.45	0.09	66	3.88	1,534	3.89	0
Insulin	68	3.46	982	1.89	0.1	57	3.35	1,333	3.38	0
Antihypertensives	276	14.04	4,560	8.77	0.17	239	14.03	5,449	13.83	0.01
Opioid analgesics	1,210	61.55	23,787	45.73	0.32	1,099	64.53	25,463	64.64	0
Triptans	132	6.71	2,083	4	0.12	122	7.16	2,821	7.16	0
NSAIDs	731	37.18	14,918	28.68	0.18	675	39.64	15,711	39.88	-0.01
Obstetric conditions, N (%)										
Multifetal gestation Flag	71	3.61	2,079	4	-0.02	63	3.7	1,463	3.71	0
Potentially teratogenic medication exposures, N (%)										
Danazol	0	0	<11	0.01	-0.01	<11	0	<11	0	
Synthetic progestins	67	3.41	1,659	3.19	0.01	60	3.52	1,387	3.52	0
Methimazole	<11	0.1	38	0.07	0.01	<11	0.12	48	0.12	0
Propylthiouracil	<11	0.15	68	0.13	0.01	<11	0.18	70	0.18	0

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		SSRI		Stand Diff ⁽¹⁾	Duloxetine		SSRI		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Corticosteroids	343	17.45	7,202	13.85	0.1	302	17.73	6,953	17.65	0
Fluconazole	109	5.54	2,084	4.01	0.07	94	5.52	2,144	5.44	0
Healthcare Utilization, mean (SD)										
Comorbidity Index	1.56	1.83	1.23	1.61	0.19	1.6	1.87	1.6	1.84	0
Morphine equivalents	24772.14	555308.29	3417.44	162034.31	0.05	27456.17	595527.12	17331.44	358985.02	0.02
Number of diagnoses	5.85	4.56	5	4.36	0.19	6.26	4.61	6.28	4.65	0
Number of ED visits	0.72	1.31	0.62	1.43	0.07	0.78	1.32	0.82	1.68	-0.03
Number of generics dispensed	5.4	4.07	4.47	3.65	0.24	5.64	4.13	6.08	4.57	-0.1
Number of hospitalizations	0.05	0.25	0.06	0.28	-0.06	0.05	0.26	0.05	0.26	0
Number of outpatient visits	5.35	6.03	4.33	5.49	0.18	5.74	6.22	5.72	6.17	0
Number of psychiatric hospitalizations	0.03	0.2	0.03	0.2	0.01	0.03	0.21	0.03	0.23	0
Number of psychiatrist visits	2.06	4.75	1.7	4.5	0.08	2.27	4.95	2.23	4.78	0.01

(1) The standardized difference is estimated as $\frac{\bar{X}_{exp} - \bar{X}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$, where s^2 represents the sample variance in the duloxetine exposed and the reference group

sTable 6 Cohort characteristics of pregnancies with exposure to duloxetine versus exposure to venlafaxine during the first trimester

	Unadjusted				Stand Diff ⁽¹⁾	Accounting for Propensity Score Strata				Stand Diff ⁽¹⁾	
	Duloxetine		Venlafaxine			N/Mean	%/SD	Duloxetine		Stand Diff ⁽¹⁾	
	N/Mean	%/SD	N/Mean	%/SD				N/Mean	%/SD		
Total	2,467	100	6,369	100		2,160	100	5,085	100		
Age, mean (SD)	27.74	5.53	26.75	5.3	0.18	27.78	5.54	27.76	5.55	0	
Race, N (%)											
White	1,950	79.04	5,140	80.7	-0.04	1,710	79.17	4,014	78.94	0.01	
Black or African American	215	8.72	456	7.16	0.06	189	8.75	442	8.68	0	
Hispanic or Latino	67	2.72	286	4.49	-0.1	59	2.73	136	2.68	0	
Asian or Other Pacific Islander	28	1.13	78	1.22	-0.01	26	1.2	71	1.4	-0.02	
American Indian	33	1.34	77	1.21	0.01	29	1.34	70	1.38	0	
Other	117	4.74	194	3.05	0.09	100	4.63	239	4.7	0	
Unknown	57	2.31	138	2.17	0.01	47	2.18	113	2.22	0	
Chronic comorbid conditions, N (%)											
Hypertension	188	7.62	335	5.26	0.1	169	7.82	440	8.65	-0.03	
Diabetes	150	6.08	235	3.69	0.11	131	6.06	332	6.54	-0.02	
Renal Disease	22	0.89	33	0.52	0.04	21	0.97	51	1	0	
Obesity Overweight	148	6	280	4.4	0.07	138	6.39	345	6.78	-0.02	
Infections, N (%)											
Toxoplasmosis	0	0	<11	0.03	-0.03	0	0	0	0		
Rubella	0	0	0	0		0	0	0	0		
Cytomegalovirus	0	0	0	0		0	0	0	0		
Herpes	39	1.58	81	1.27	0.03	33	1.53	75	1.47	0	
Syphilis	<11	0	<11	0.05	-0.03	0	0	0	0		
Varicella	<11	0.04	<11	0.03	0	0	0	0	0		
Parvovirus B19	0	0	0	0		0	0	0	0		

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Zika virus other mosquito	0	0	0	0		0	0	0	0	
Lymphocytic choriomeningitis	0	0.04	<11	0	0.03	0	0	0	0	
Influenza	20	0.81	58	0.91	-0.01	18	0.83	41	0.8	0
Chlamydia	11	0.45	30	0.47	0	<11	0.46	26	0.51	-0.01
Human papilloma virus	23	0.93	47	0.74	0.02	20	0.93	46	0.9	0
Gonorrhea	13	0.53	21	0.33	0.03	<11	0.46	23	0.44	0
HIV	<11	0.28	24	0.38	-0.02	<11	0.28	15	0.3	0
Trichomoniasis	18	0.73	61	0.96	-0.02	16	0.74	35	0.69	0.01
Indications for duloxetine, N (%)										
Depression	1,201	48.68	3,130	49.14	-0.01	1,198	55.46	2,904	57.11	-0.03
Anxiety	750	30.4	1,785	28.03	0.05	749	34.68	1,868	36.73	-0.04
Neuropathic Pain	253	10.26	352	5.53	0.18	249	11.53	576	11.33	0.01
Fibromyalgia	254	10.3	217	3.41	0.28	250	11.57	559	11	0.02
Non neuropathic Pain	1,200	48.64	2,250	35.33	0.27	1,196	55.37	2,800	55.06	0.01
Other psychiatric conditions, N (%)										
Sleep disorder	140	5.67	344	5.4	0.01	132	6.11	313	6.16	0
Bipolar disorder	317	12.85	663	10.41	0.08	282	13.06	697	13.72	-0.02
Psychosis	20	0.81	58	0.91	-0.01	19	0.88	55	1.08	-0.02
Schizophrenia	23	0.93	57	0.89	0	21	0.97	59	1.16	-0.02
Personality disorder	53	2.15	112	1.76	0.03	52	2.41	136	2.67	-0.02
Adjustment disorder	27	1.09	69	1.08	0	23	1.06	52	1.03	0
Tobacco use, N (%)	273	11.07	588	9.23	0.06	258	11.94	603	11.86	0
Alcohol abuse or dependence, N (%)	31	1.26	117	1.84	-0.05	28	1.3	69	1.35	0
Drug abuse or dependence, N (%)	81	3.28	255	4	-0.04	77	3.56	189	3.72	-0.01

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Other medication exposures, N (%)										
Benzodiazepines	946	38.35	1,966	30.87	0.16	877	40.6	2,130	41.88	-0.03
Other hypnotics	584	23.67	1,115	17.51	0.15	538	24.91	1,331	26.18	-0.03
Barbiturates	118	4.78	228	3.58	0.06	103	4.77	246	4.84	0
Anxiolytics	124	5.03	280	4.4	0.03	113	5.23	293	5.76	-0.02
Anticonvulsants	622	25.21	1,031	16.19	0.22	568	26.3	1,316	25.88	0.01
Antipsychotics	487	19.74	1,007	15.81	0.1	448	20.74	1,122	22.06	-0.03
SSRIs	677	27.44	1,587	24.92	0.06	615	28.47	1,483	29.16	-0.02
SNRIs	38	1.54	6,369	100	-11.3	34	1.57	5,085	100	-11.18
Other Antidep	695	28.17	1,520	23.87	0.1	641	29.68	1,521	29.92	-0.01
Stimulants	192	7.78	370	5.81	0.08	166	7.69	390	7.67	0
Antidiabetic	98	3.97	172	2.7	0.07	84	3.89	204	4.02	-0.01
Insulin	80	3.24	113	1.77	0.09	68	3.15	166	3.27	-0.01
Antihypertensives	362	14.67	630	9.89	0.15	317	14.68	742	14.59	0
Opioid analgesics	1,513	61.33	3,138	49.27	0.24	1,381	63.94	3,231	63.54	0.01
Triptans	174	7.05	341	5.35	0.07	160	7.41	391	7.69	-0.01
NSAIDs	936	37.94	1,880	29.52	0.18	868	40.19	2,053	40.37	0
Obstetric conditions, N (%)										
Multifetal gestation Flag	86	3.49	244	3.83	-0.02	76	3.52	178	3.51	0
Potentially teratogenic medication exposures, N (%)										
Danazol	<11	0	<11	0		0	0	0	0	
Synthetic progestins	85	3.45	206	3.23	0.01	79	3.66	193	3.8	-0.01
Methimazole	<11	0.12	<11	0.09	0.01	<11	0.14	<11	0.13	0
Propylthiouracil	<11	0.16	<11	0.16	0	<11	0.19	<11	0.17	0

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾	Duloxetine		Venlafaxine		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Corticosteroids	439	17.79	909	14.27	0.1	386	17.87	903	17.75	0
Fluconazole	130	5.27	253	3.97	0.06	112	5.19	253	4.98	0.01
Healthcare Utilization, mean (SD)										
Comorbidity Index	1.57	1.83	1.32	1.64	0.14	1.61	1.86	1.57	1.77	0.02
Morphine equivalents	20232.43	495794.92	2551.52	86147.49	0.05	12168.33	251960.54	7875.27	185277.7	0.02
Number of diagnoses	5.91	4.6	5.14	4.34	0.17	6.28	4.65	6.36	4.79	-0.02
Number of ED visits	0.71	1.29	0.62	1.36	0.07	0.76	1.31	0.83	1.61	-0.05
Number of generics dispensed	5.58	4.15	5.18	3.9	0.1	5.82	4.21	6.43	4.86	-0.13
Number of hospitalizations	0.05	0.26	0.05	0.27	-0.01	0.06	0.27	0.06	0.27	0
Number of outpatient visits	5.52	6.27	4.66	5.84	0.14	5.88	6.45	5.82	5.92	0.01
Number of psychiatric hospitalizations	0.03	0.22	0.03	0.21	0.01	0.04	0.23	0.04	0.22	0.01
Number of psychiatrist visits	2.23	4.77	2.03	4.76	0.04	2.43	4.91	2.43	4.76	0

(1) The standardized difference is estimated as $\frac{\bar{X}_{exp} - \bar{X}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$, where s^2 represents the sample variance in the duloxetine exposed and the reference group.

sTable 7 Cohort characteristics of pregnancies with exposure to duloxetine during the first trimester versus duloxetine discontinuers (i.e., exposure before but not during the first trimester)

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Total	2,532	100	2,456	100		2,215	100	1,978	100	
Age, mean (SD)	27.75	5.53	26.67	5.25	0.12	27.81	5.55	27.93	5.56	-0.02
Race, N (%)										
White	2,003	79.11	1,866	75.98	0.08	1,755	79.23	1,572	79.49	-0.01
Black or African American	219	8.65	260	10.59	-0.07	192	8.67	173	8.74	0
Hispanic or Latino	70	2.76	78	3.18	-0.02	61	2.75	53	2.66	0.01
Asian or Other Pacific Islander	32	1.26	39	1.59	-0.03	30	1.35	30	1.52	-0.01
American Indian	33	1.3	42	1.71	-0.03	28	1.26	25	1.24	0
Other	117	4.62	132	5.37	-0.03	101	4.56	85	4.3	0.01
Unknown	58	2.29	39	1.59	0.05	48	2.17	41	2.06	0.01
Chronic comorbid conditions, N (%)										
Hypertension	191	7.54	145	5.9	0.07	173	7.81	161	8.15	-0.01
Diabetes	152	6	117	4.76	0.05	135	6.09	119	6	0
Renal Disease	23	0.91	25	1.02	-0.01	22	0.99	21	1.07	-0.01
Obesity Overweight	152	6	128	5.21	0.03	142	6.41	129	6.51	0
Infections, N (%)										
Toxoplasmosis	0	0	0	0		0	0	0	0	
Rubella	0	0	0	0		0	0	0	0	
Cytomegalovirus	0	0	0	0		0	0	0	0	
Herpes	41	1.62	27	1.1	0.04	35	1.58	31	1.59	0
Syphilis	<11	0	<11	0.08	-0.04	0	0	0	0	
Varicella	<11	0.04	<11	0	0.03	0	0	0	0	

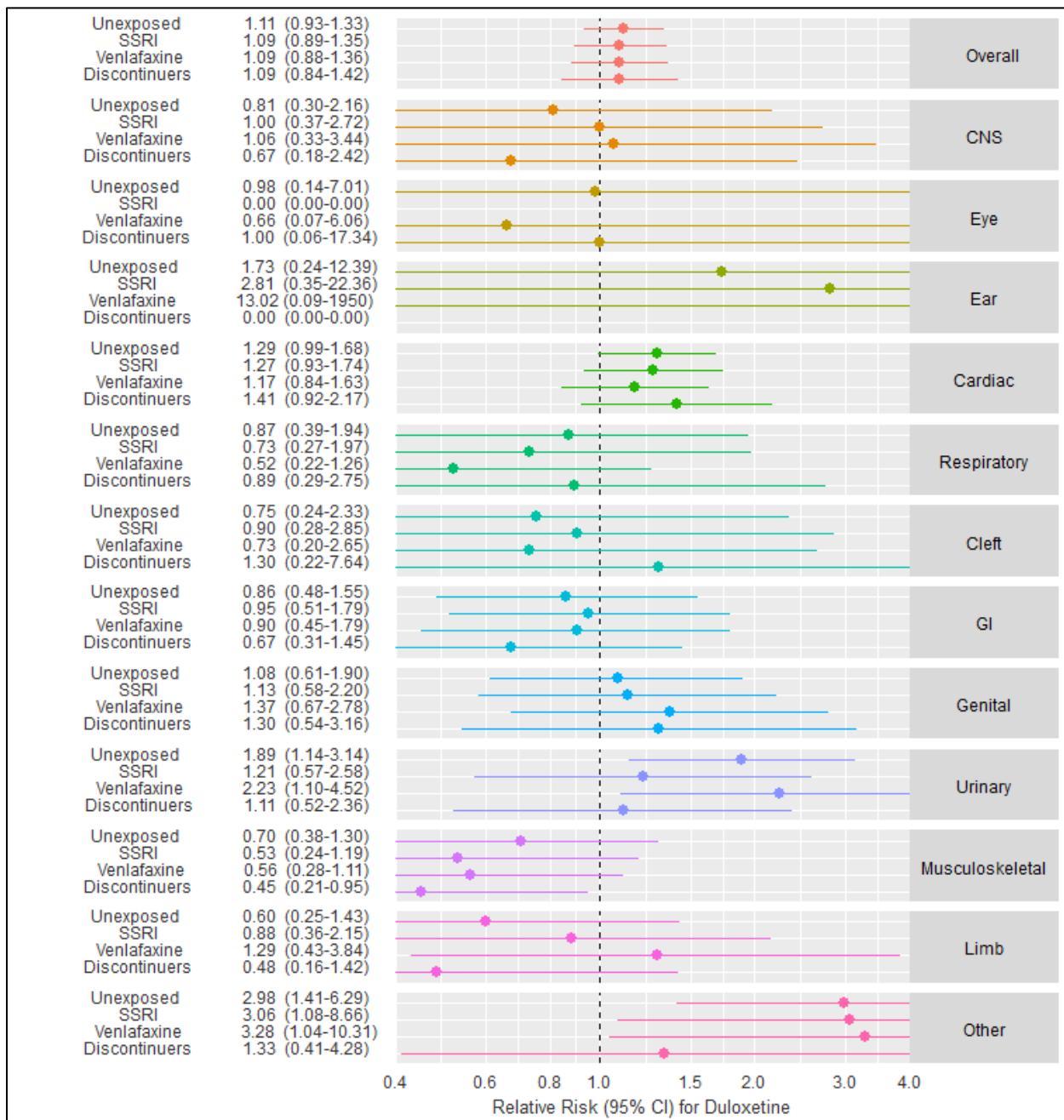
	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Parvovirus B19	0	0	0	0		0	0	0	0	
Zika virus other mosquito	0	0	0	0		0	0	0	0	
Lymphocytic choriomeningitis	<11	0.04	0	0	0.03	0	0	0	0	
Influenza	21	0.83	29	1.18	-0.04	19	0.86	16	0.82	0
Chlamydia	11	0.43	13	0.53	-0.01	<11	0.45	<11	0.49	-0.01
Human papilloma virus	25	0.99	18	0.73	0.03	22	0.99	16	0.83	0.02
Gonorrhea	13	0.51	15	0.61	-0.01	<11	0.45	<11	0.5	-0.01
HIV	<11	0.28	11	0.45	-0.03	<11	0.27	<11	0.23	0.01
Trichomoniasis	18	0.71	32	1.3	-0.06	16	0.72	14	0.73	0
Indications for duloxetine, N (%)										
Depression	1,235	48.78	943	38.4	0.21	1,232	55.62	1,100	55.6	0
Anxiety	778	30.73	601	24.47	0.14	774	34.94	701	35.46	-0.01
Neuropathic Pain	267	10.55	228	9.28	0.04	267	12.05	257	12.97	-0.03
Fibromyalgia	264	10.43	187	7.61	0.1	262	11.83	240	12.13	-0.01
Non neuropathic Pain	1,234	48.74	1,104	44.95	0.08	1,227	55.4	1,117	56.49	-0.02
Other psychiatric conditions, N (%)										
Sleep disorder	144	5.69	121	4.93	0.03	134	6.05	122	6.15	0
Bipolar disorder	330	13.03	260	10.59	0.08	293	13.23	274	13.84	-0.02
Psychosis	20	0.79	21	0.86	-0.01	19	0.86	16	0.79	0.01
Schizophrenia	25	0.99	19	0.77	0.02	23	1.04	21	1.05	0
Personality disorder	56	2.21	41	1.67	0.04	55	2.48	49	2.47	0
Adjustment disorder	29	1.15	16	0.65	0.05	25	1.13	20	1.03	0.01
Tobacco use, N (%)	279	11.02	243	9.89	0.04	264	11.92	232	11.74	0.01
Alcohol abuse or dependence, N (%)	31	1.22	29	1.18	0	28	1.26	24	1.23	0

	Unadjusted					Accounting for Propensity Score Strata				
	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD	
Drug abuse or dependence, N (%)	84	3.32	69	2.81	0.03	79	3.57	74	3.73	-0.01
Other medication exposures, N (%)										
Benzodiazepines	979	38.67	709	28.87	0.21	909	41.04	824	41.67	-0.01
Other hypnotics	608	24.01	472	19.22	0.12	559	25.24	518	26.21	-0.02
Barbiturates	124	4.9	93	3.79	0.05	110	4.97	102	5.17	-0.01
Anxiolytics	129	5.09	99	4.03	0.05	118	5.33	107	5.4	0
Anticonvulsants	642	25.36	451	18.36	0.17	586	26.46	532	26.89	-0.01
Antipsychotics	505	19.94	376	15.31	0.12	462	20.86	409	20.66	0
SSRIs	705	27.84	579	23.57	0.1	643	29.03	591	29.87	-0.02
SNRIs	103	4.07	118	4.8	-0.04	92	4.15	86	4.36	-0.01
Other Antidep	720	28.44	527	21.46	0.16	664	29.98	593	29.99	0
Stimulants	198	7.82	129	5.25	0.1	171	7.72	159	8.02	-0.01
Antidiabetic	100	3.95	63	2.57	0.08	86	3.88	71	3.57	0.02
Insulin	80	3.16	66	2.69	0.03	69	3.12	67	3.39	-0.02
Antihypertensives	373	14.73	259	10.55	0.13	327	14.76	293	14.79	0
Opioid analgesics	1,554	61.37	1,419	57.78	0.07	1,418	64.02	1,292	65.32	-0.03
Triptans	178	7.03	139	5.66	0.06	164	7.4	147	7.41	0
NSAIDs	958	37.84	805	32.78	0.11	889	40.14	783	39.57	0.01
Obstetric conditions, N (%)										
Multifetal gestation Flag	87	3.44	86	3.5	0	77	3.48	67	3.4	0
Potentially teratogenic medication exposures, N (%)										
Danazol	<11	0	<11	0		0	0	0	0	.
Synthetic progestins	88	3.48	66	2.69	0.05	80	3.61	73	3.67	0
Methimazole	<11	0.12	<11	0.04	0.03	<11	0.14	<11	0.09	0.01

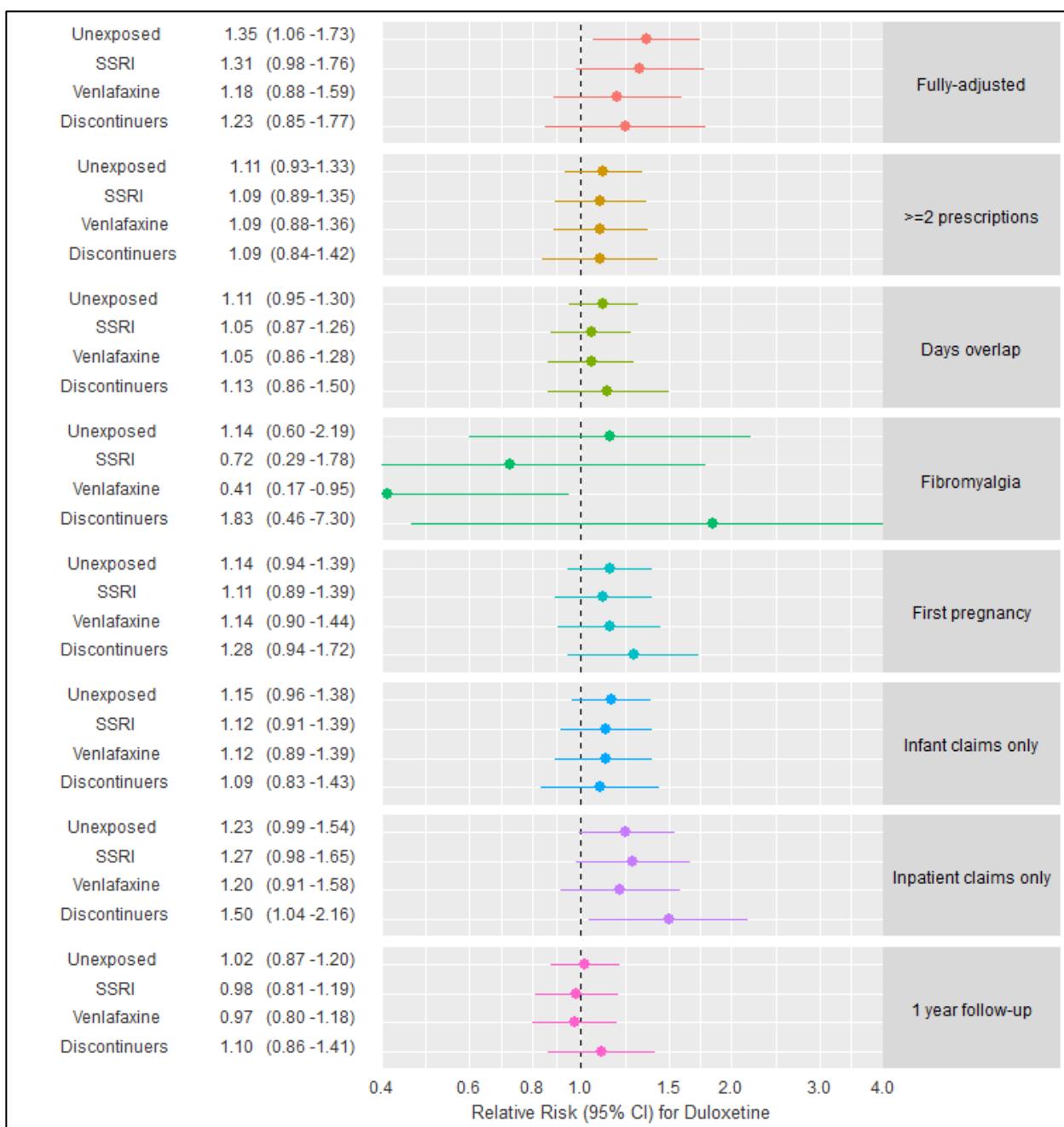
	Unadjusted					Accounting for Propensity Score Strata					
	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾	Duloxetine		Discontinuers		Stand Diff ⁽¹⁾	
	N/Mean	%/SD	N/Mean	%/SD		N/Mean	%/SD	N/Mean	%/SD		
Propylthiouracil	<11	0.16	<11	0.08	0.02	<11	0.18	<11	0.09	0.02	
Corticosteroids	453	17.89	373	15.19	0.07	401	18.1	353	17.83	0.01	
Fluconazole	133	5.25	94	3.83	0.07	115	5.19	114	5.74	-0.02	
Healthcare Utilization, mean (SD)											
Comorbidity Index	1.58	1.85	1.36	1.7	0.12	1.62	1.89	1.62	1.89	0	
Morphine equivalents	19773.7	489395.76	5061.95	60497.3	0.04	7127.54	103333.53	7473.86	75448.41	0	
Number of diagnoses	5.95	4.65	5.8	4.59	0.03	6.33	4.7	6.54	4.87	-0.04	
Number of ED visits	0.72	1.3	0.81	1.64	-0.06	0.77	1.32	0.83	1.66	-0.04	
Number of generics dispensed	5.63	4.19	5.11	4.11	0.12	5.87	4.25	6.1	4.53	-0.05	
Number of hospitalizations	0.05	0.27	0.05	0.28	0	0.06	0.28	0.06	0.27	0	
Number of outpatient visits	5.58	6.43	5.2	6.2	0.06	5.97	6.63	6.1	6.59	-0.02	
Number of psychiatric hospitalizations	0.04	0.22	0.04	0.24	-0.01	0.04	0.23	0.04	0.22	0	
Number of psychiatrist visits	2.28	4.94	1.95	4.62	0.07	2.49	5.1	2.52	5.09	-0.01	

(1) The standardized difference is estimated as $\frac{\bar{X}_{exp} - \bar{X}_{ref}}{\sqrt{\frac{s_{exp}^2 + s_{ref}^2}{2}}}$, where s^2 represents the sample variance in the duloxetine exposed and the reference group.

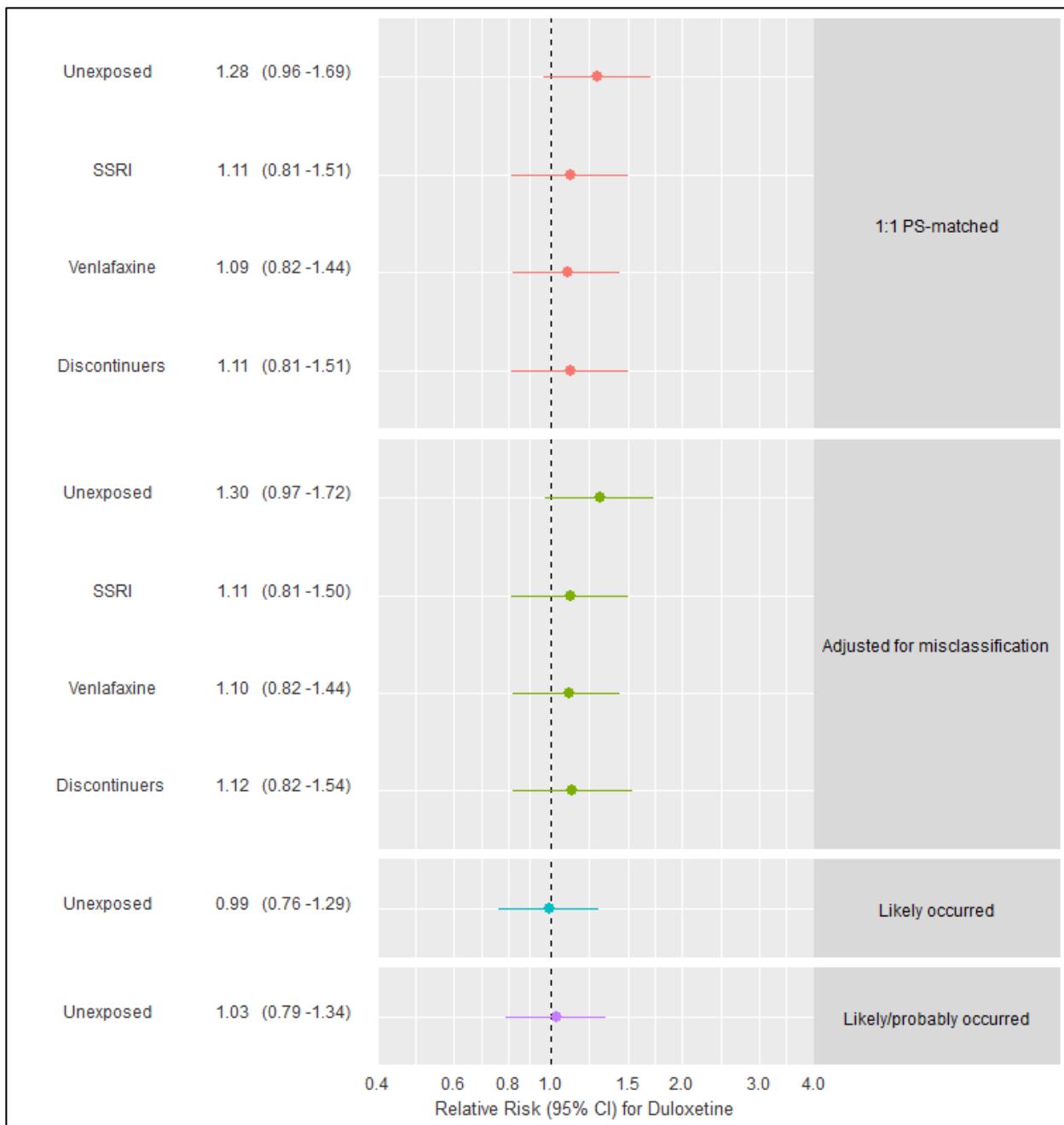
sFigure 1 Risk of congenital malformations associated with first trimester exposure to duloxetine: fully adjusted analyses



sFigure 2 Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses

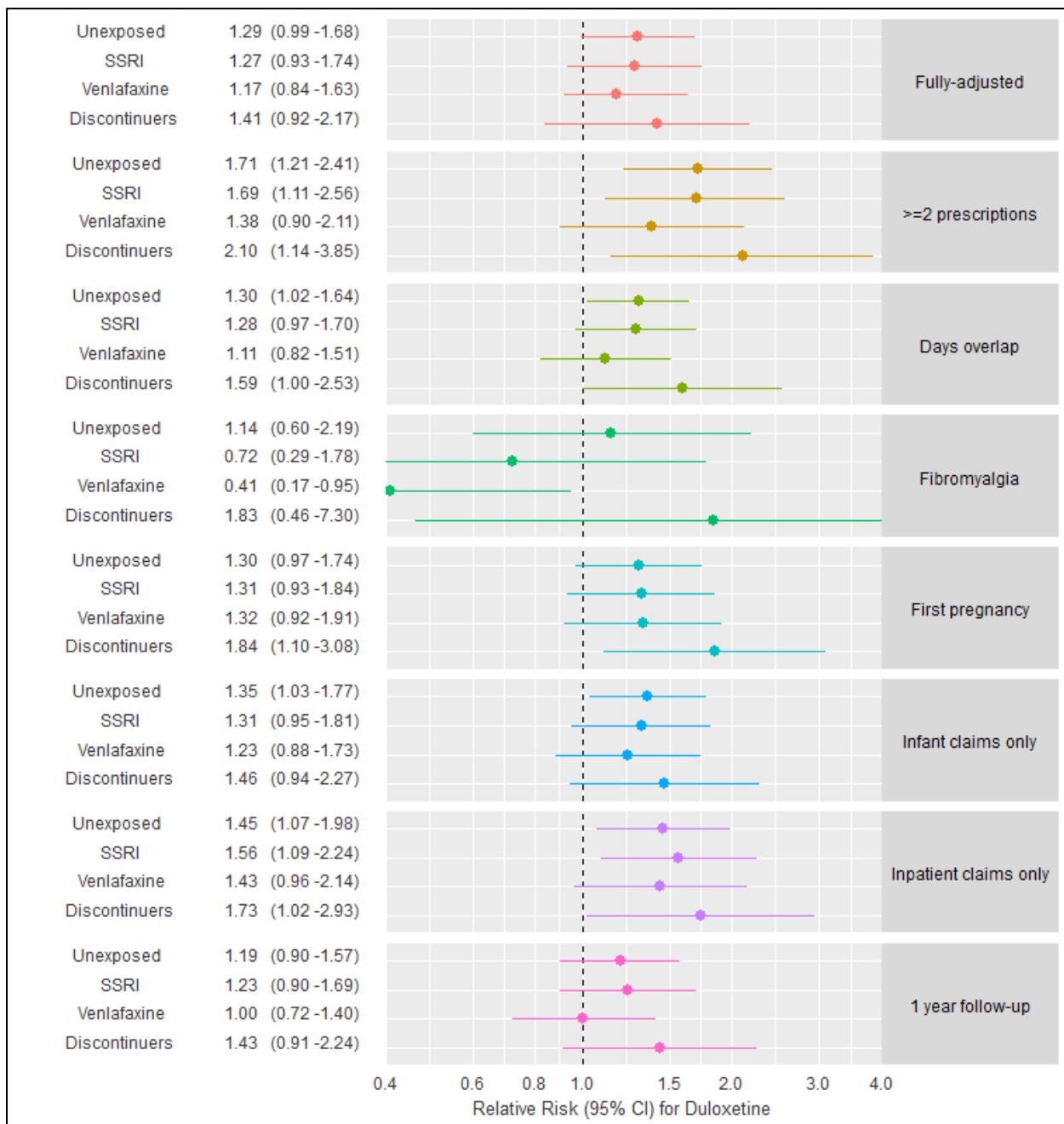


sFigure 3 Risk of any malformation associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification

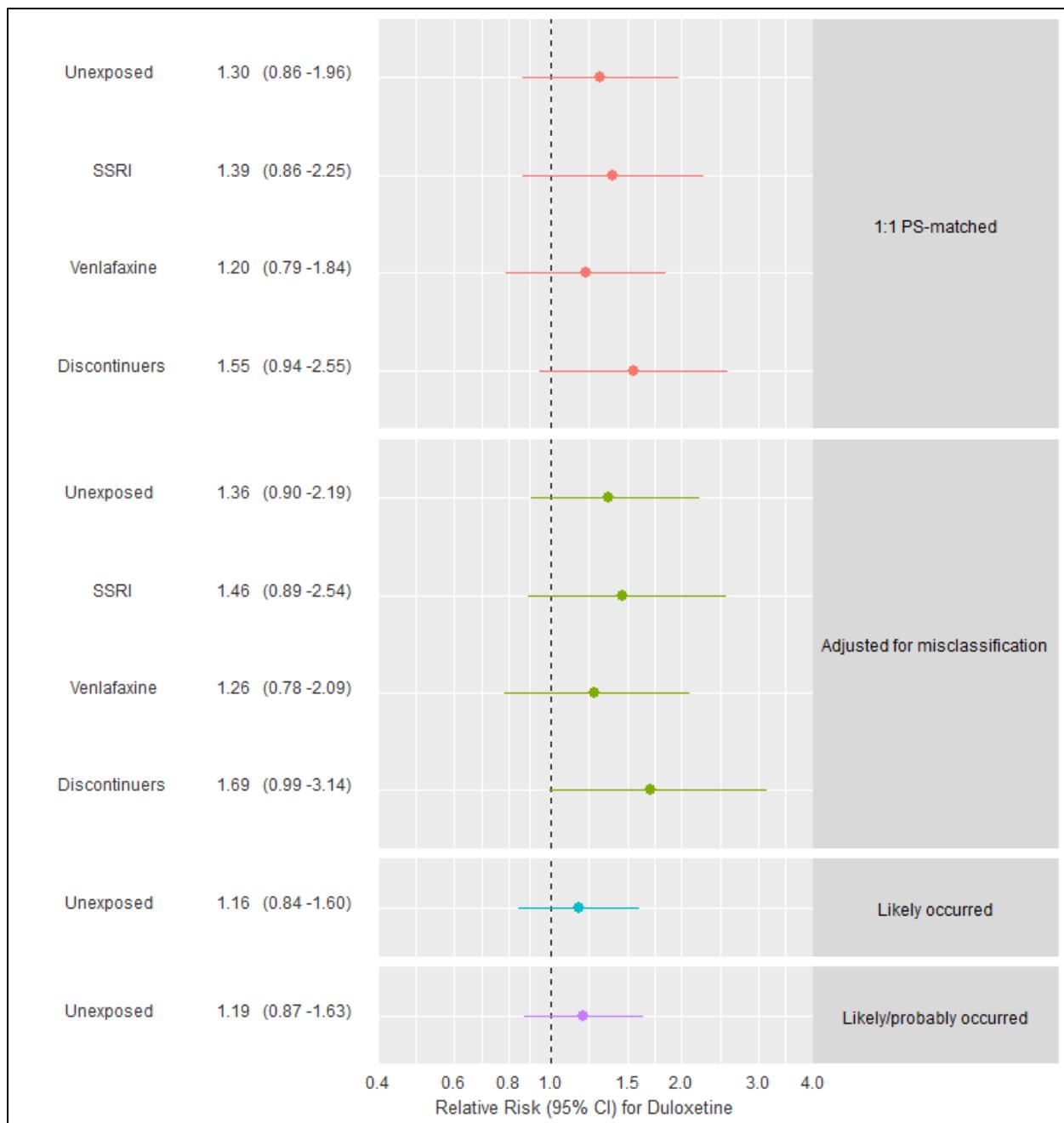


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 4 Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses

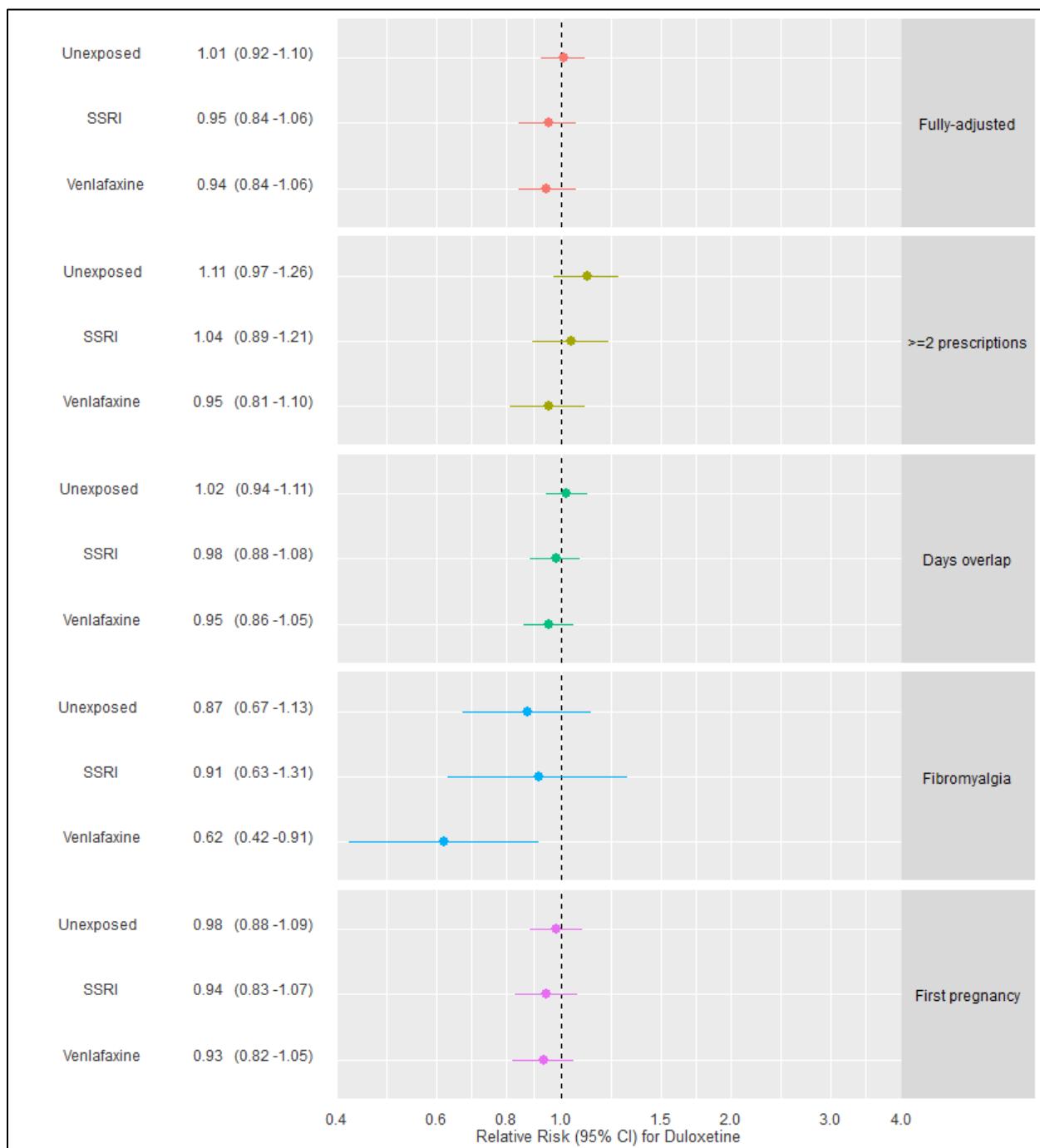


sFigure 5 Risk of cardiac malformations associated with first trimester exposure to duloxetine: sensitivity analyses to address outcome misclassification

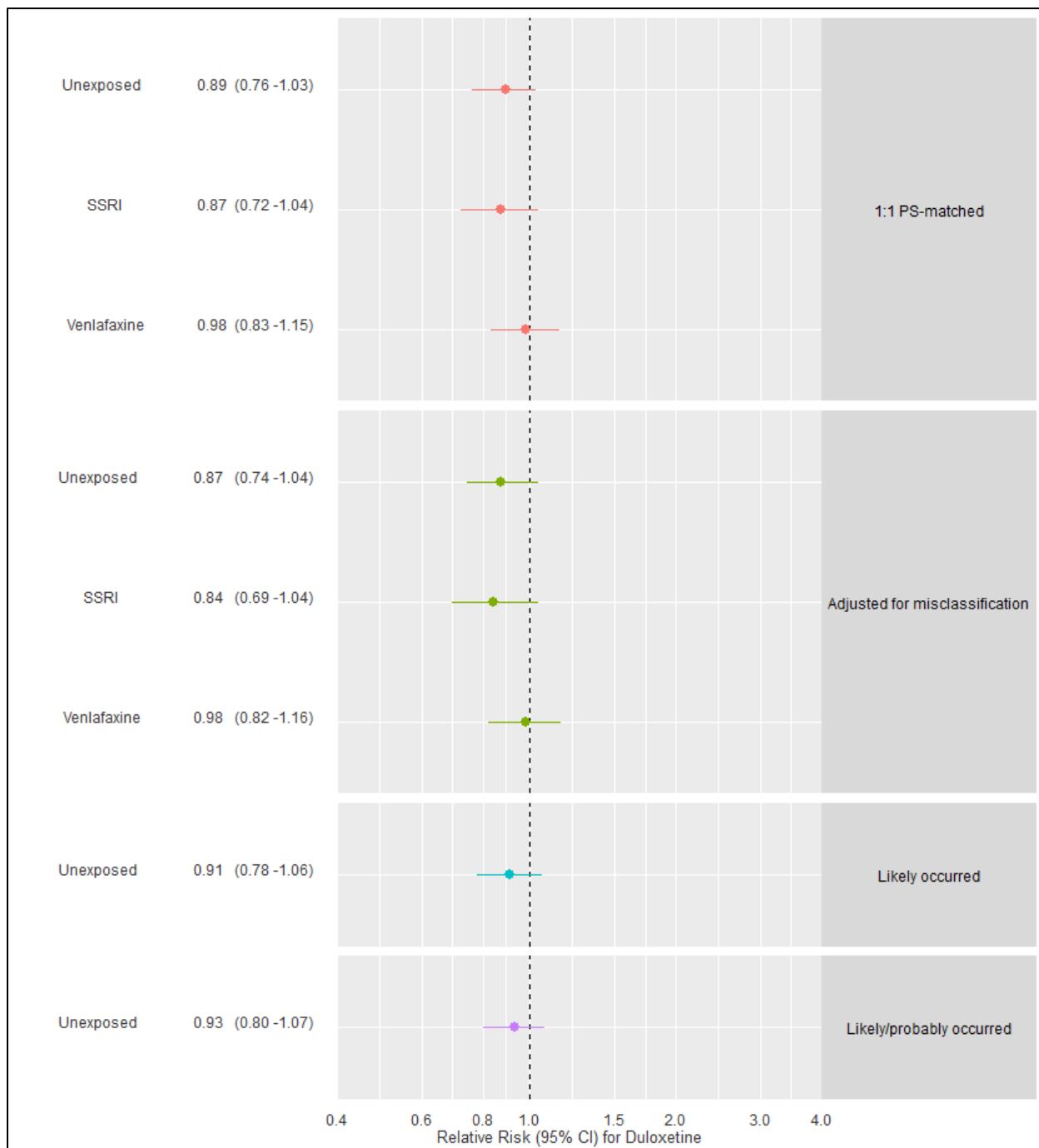


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 6 Risk of preterm birth associated with early exposure to duloxetine: sensitivity analyses

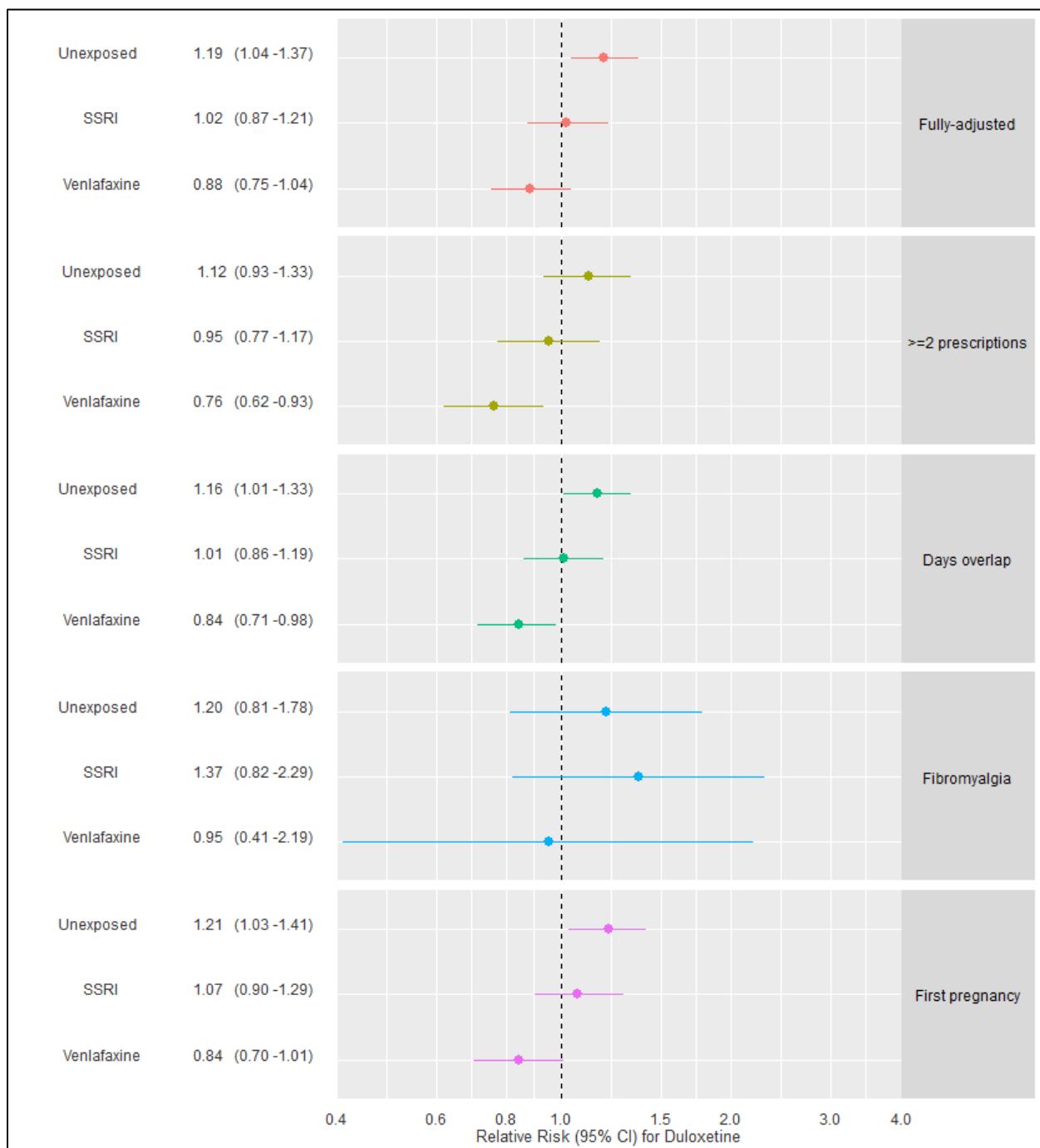


sFigure 7 Risk of preterm birth associated with early exposure to duloxetine: sensitivity analyses to address outcome misclassification

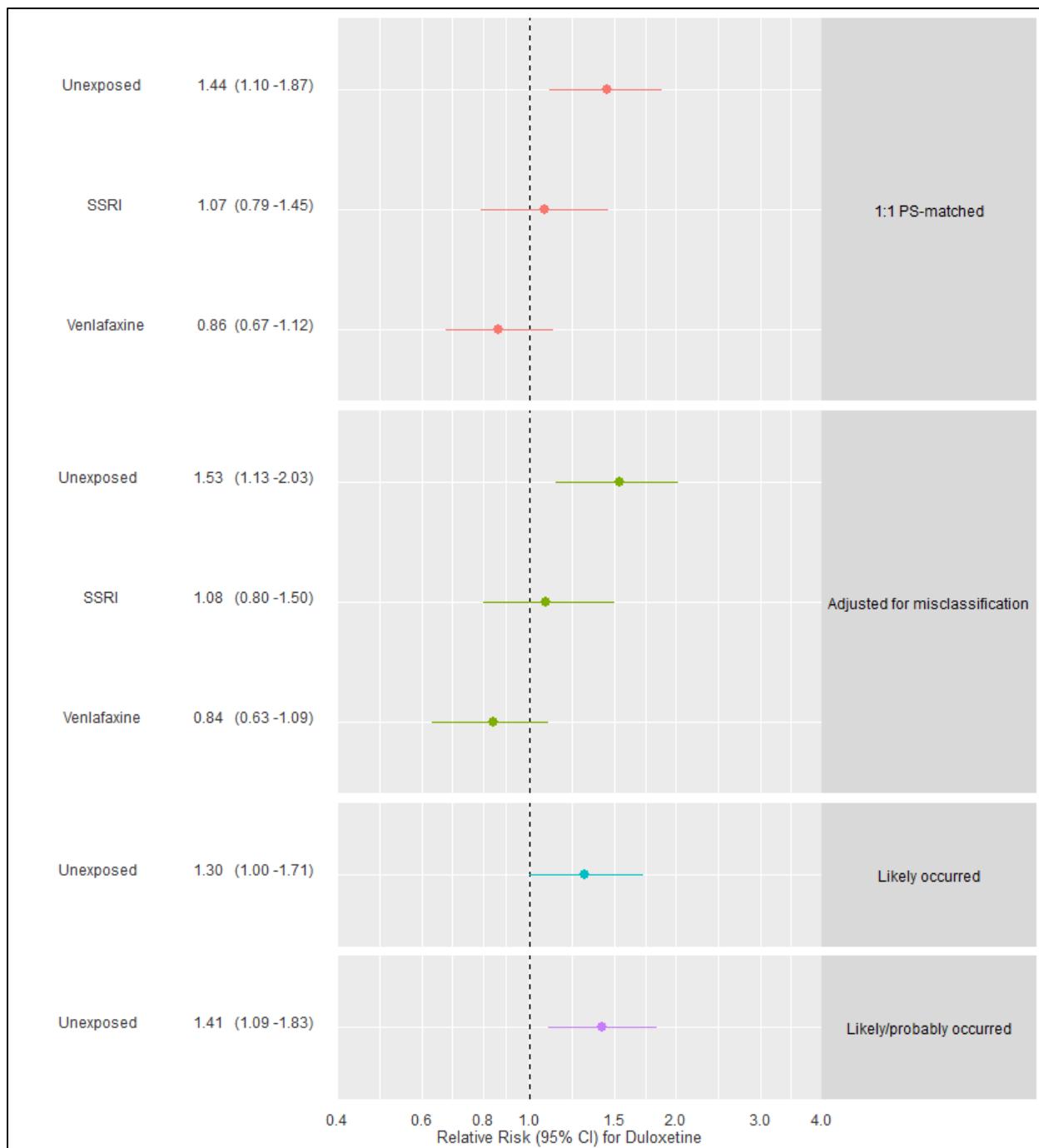


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 8 Risk of preterm birth associated with late exposure to duloxetine: sensitivity analyses

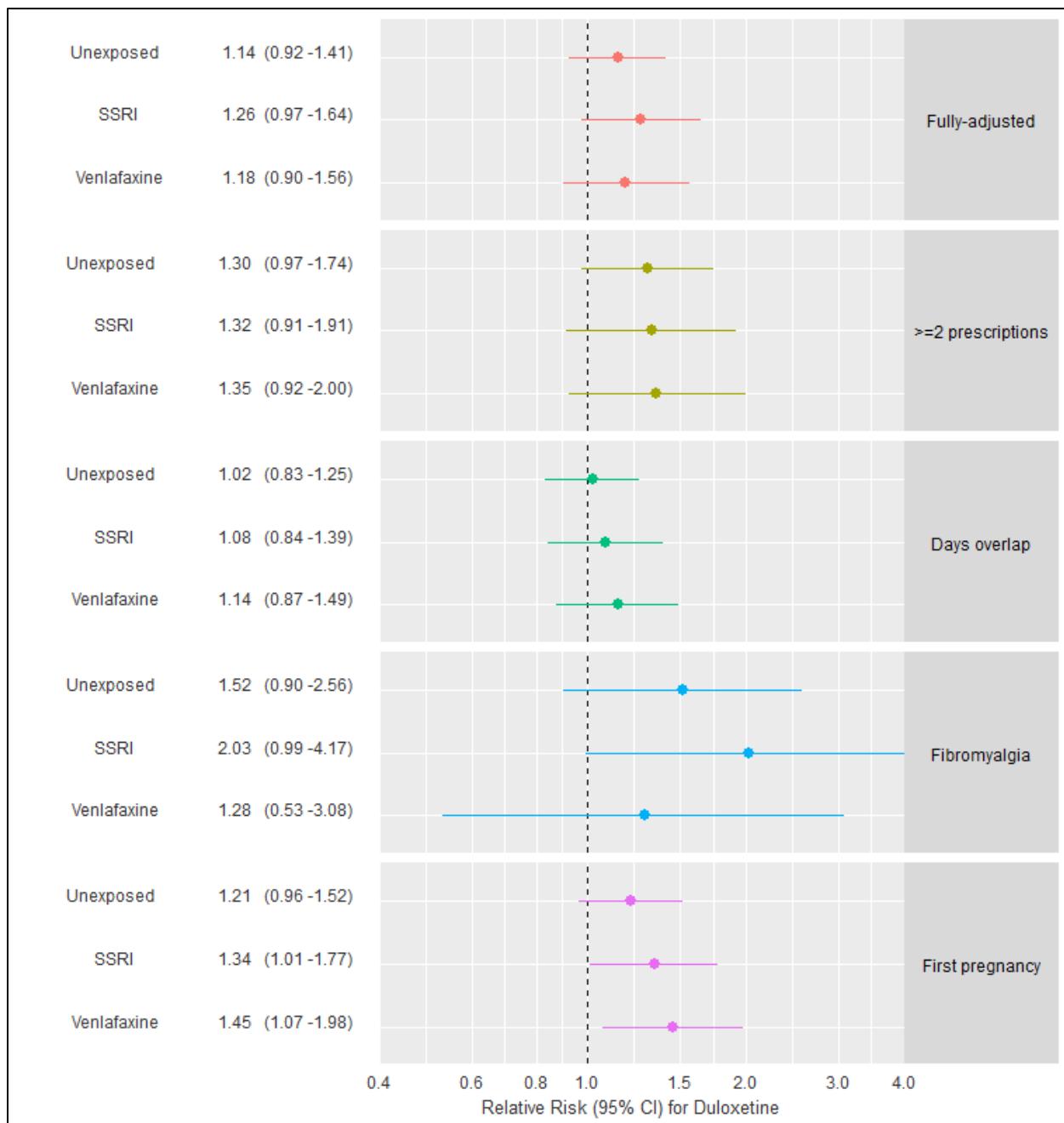


sFigure 9 Risk of preterm birth associated with late exposure to duloxetine: sensitivity analyses to address outcome misclassification

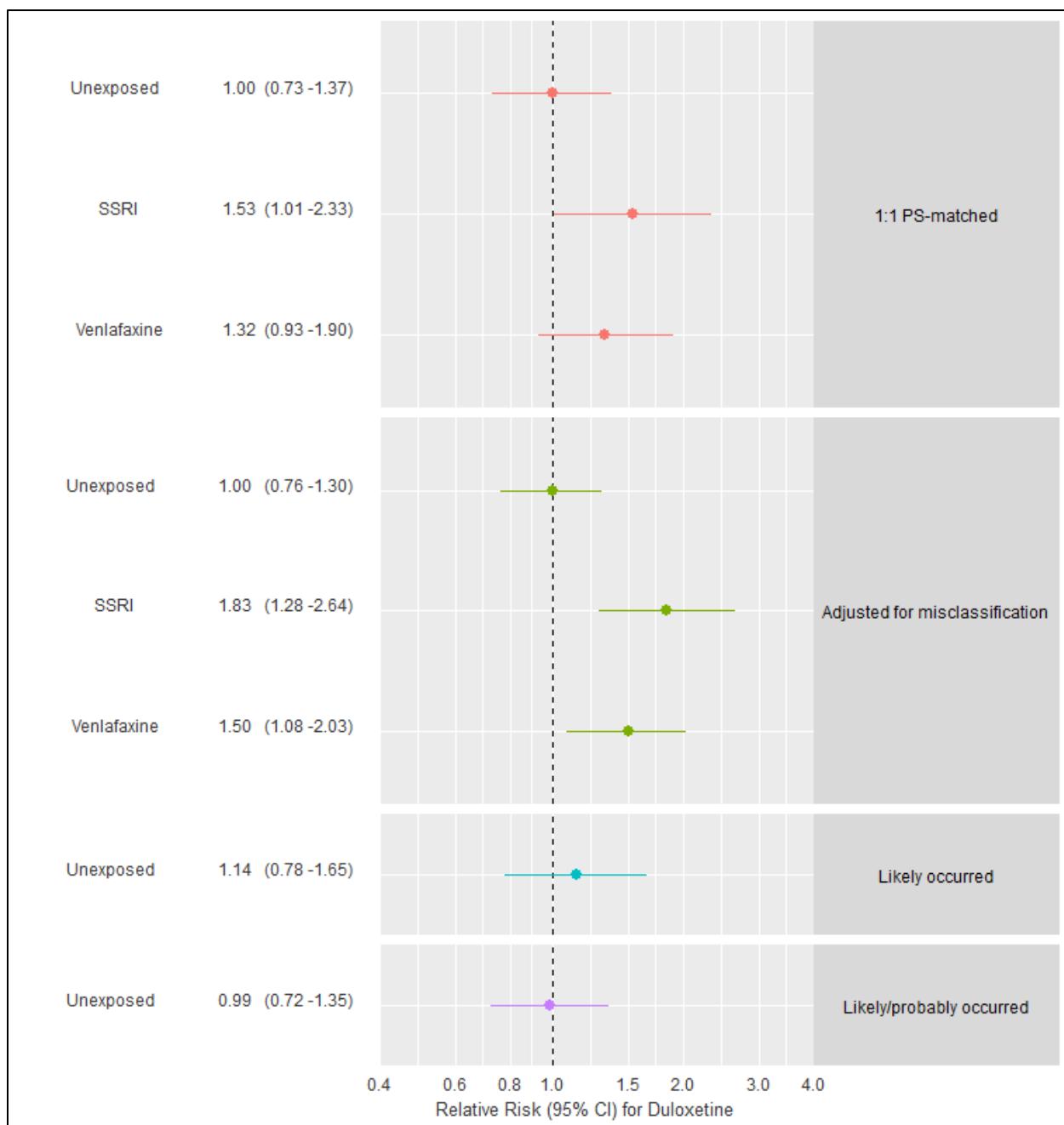


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 10 Risk of small for gestational age associated with early pregnancy exposure to duloxetine: sensitivity analyses

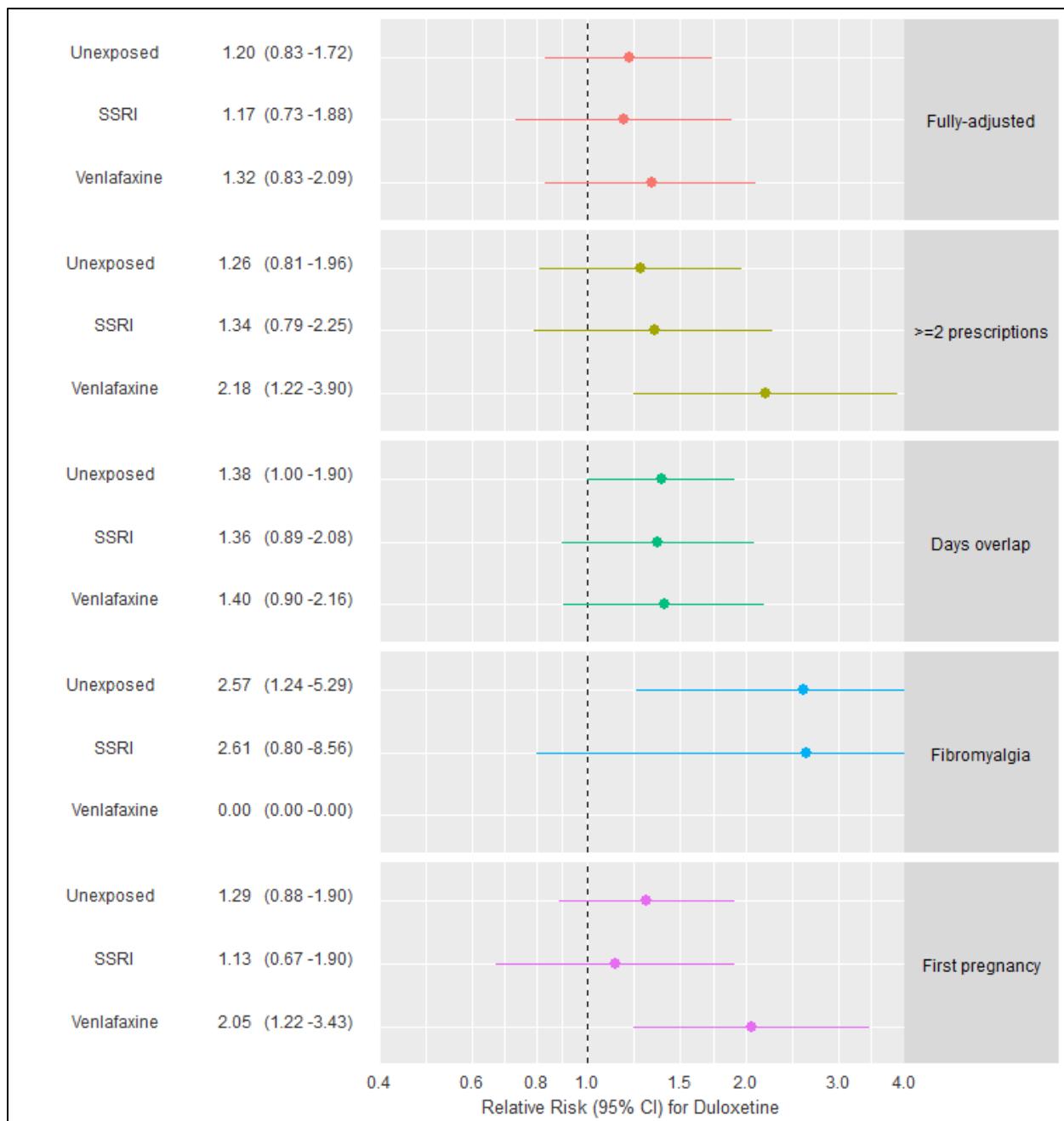


sFigure 11 Risk of small for gestational age associated with early pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

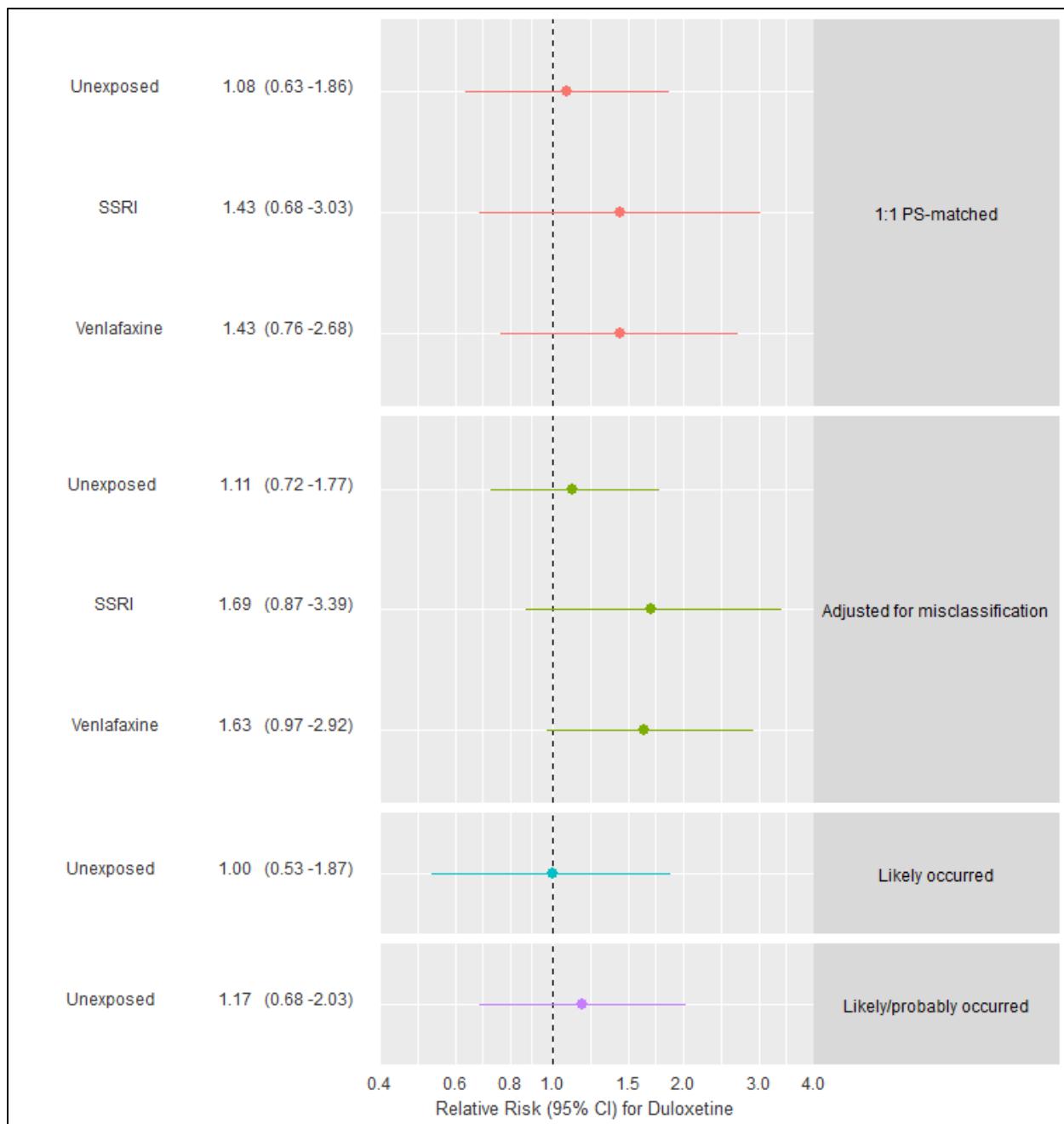


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 12 Risk of small for gestational age associated with late pregnancy exposure to duloxetine: sensitivity analyses

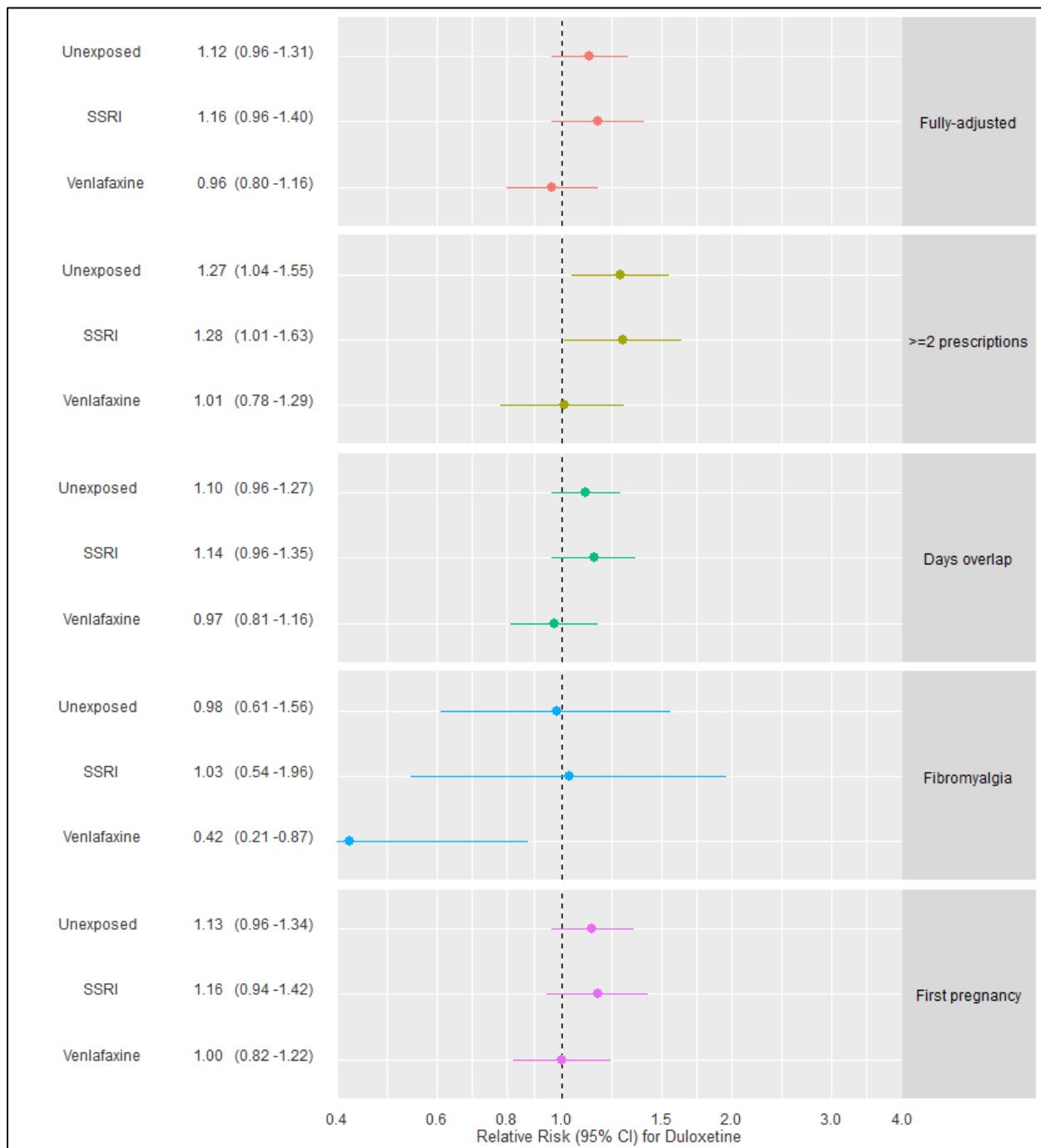


sFigure 13 Risk of small for gestational age associated with late pregnancy exposure to duloxetine: sensitivity analyses to address outcome misclassification

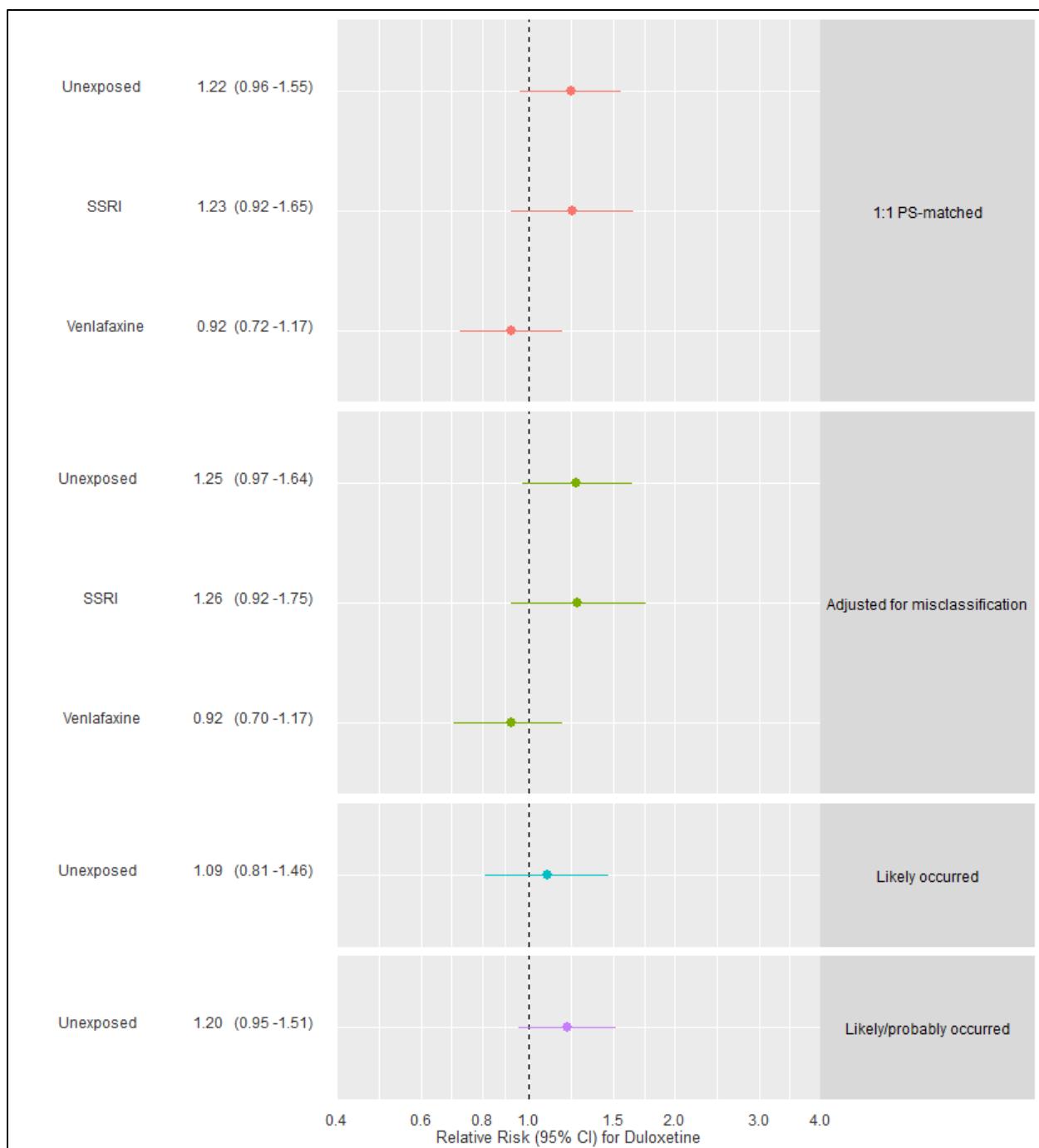


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 14 Risk of preeclampsia associated with early exposure to duloxetine: sensitivity analyses

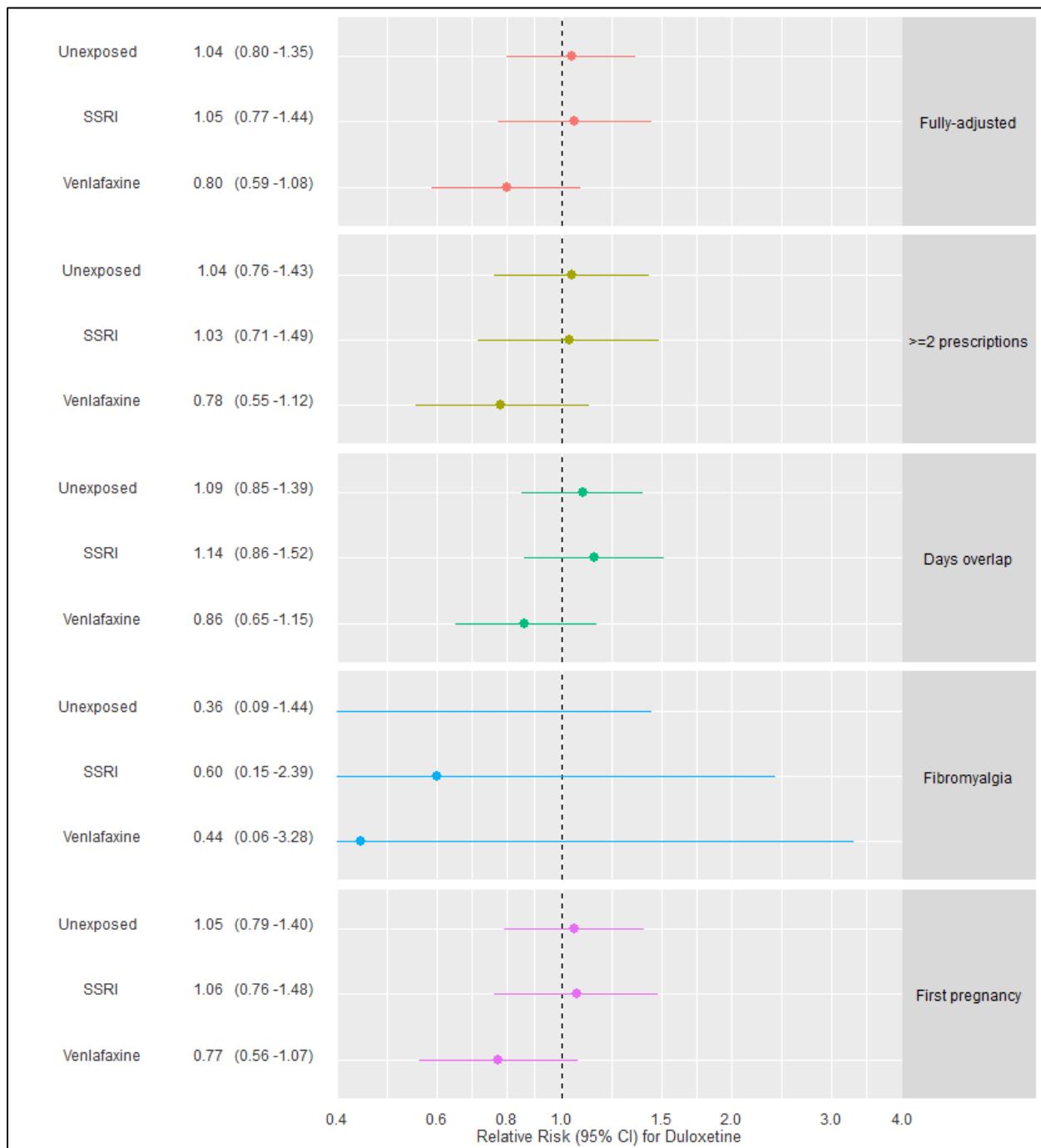


sFigure 15 Risk of preeclampsia associated with early exposure to duloxetine: sensitivity analyses to address outcome misclassification

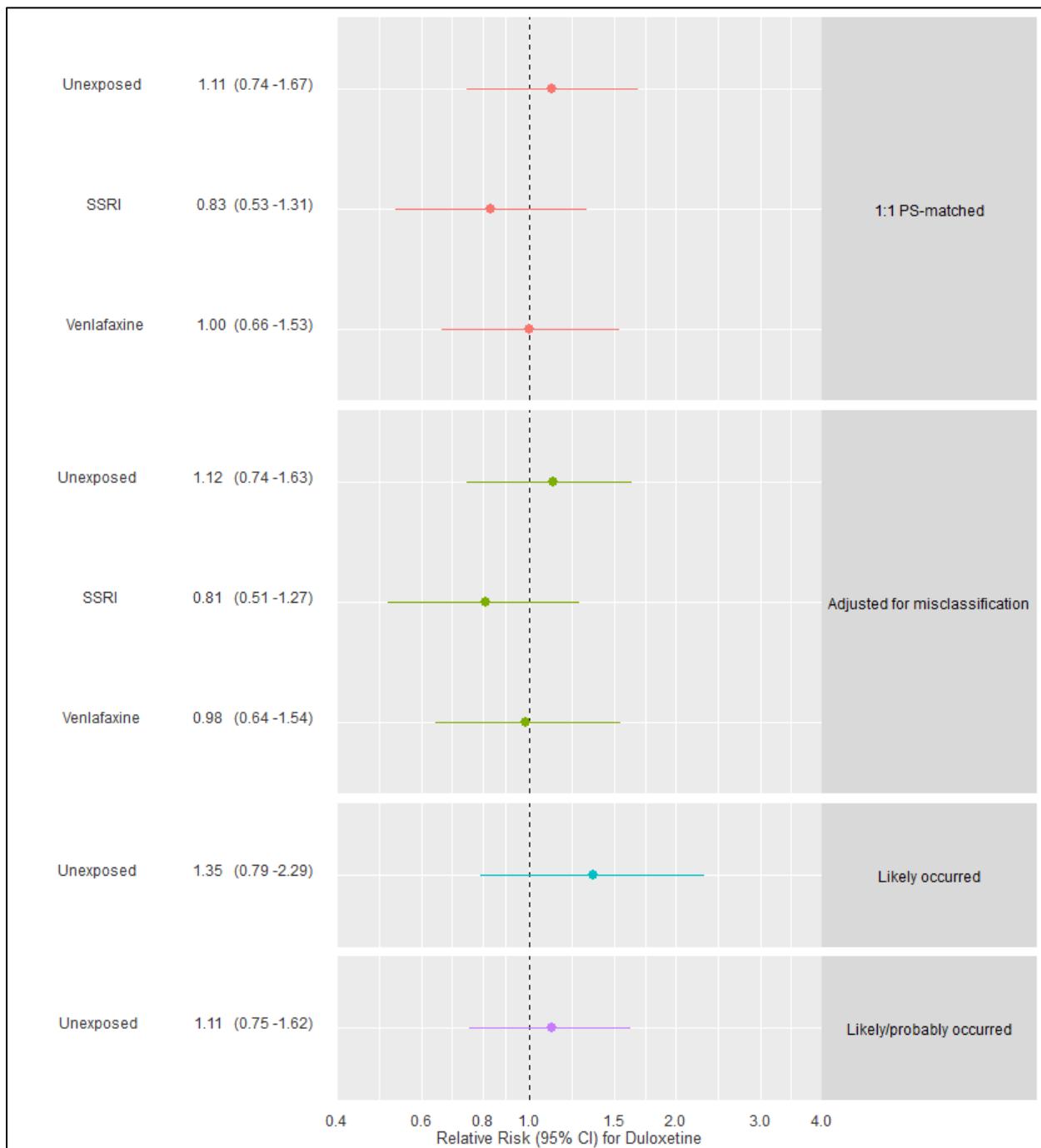


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 16 Risk of preeclampsia associated with late exposure to duloxetine: sensitivity analyses

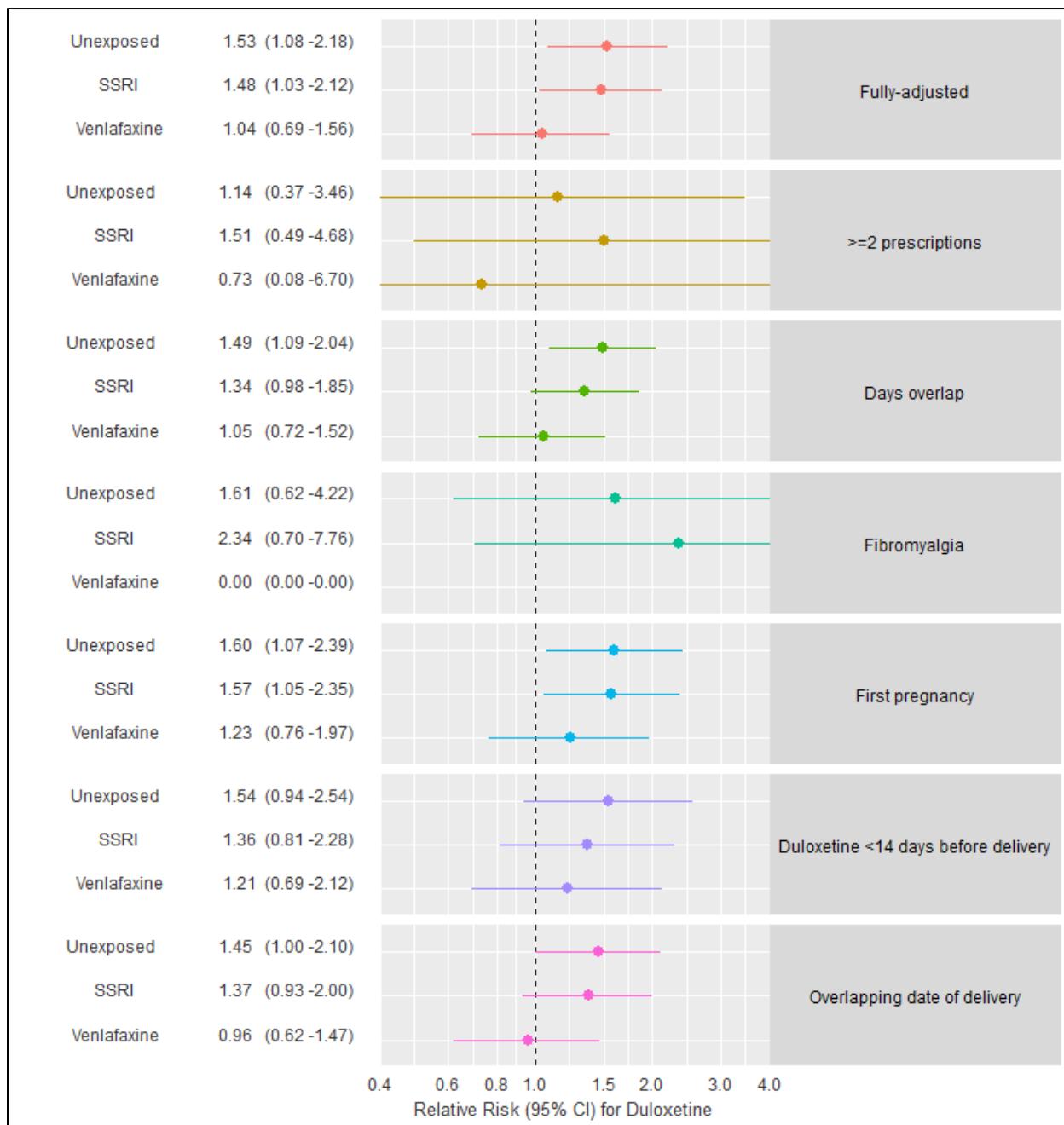


sFigure 17 Risk of preeclampsia associated with late exposure to duloxetine: sensitivity analyses to address outcome misclassification

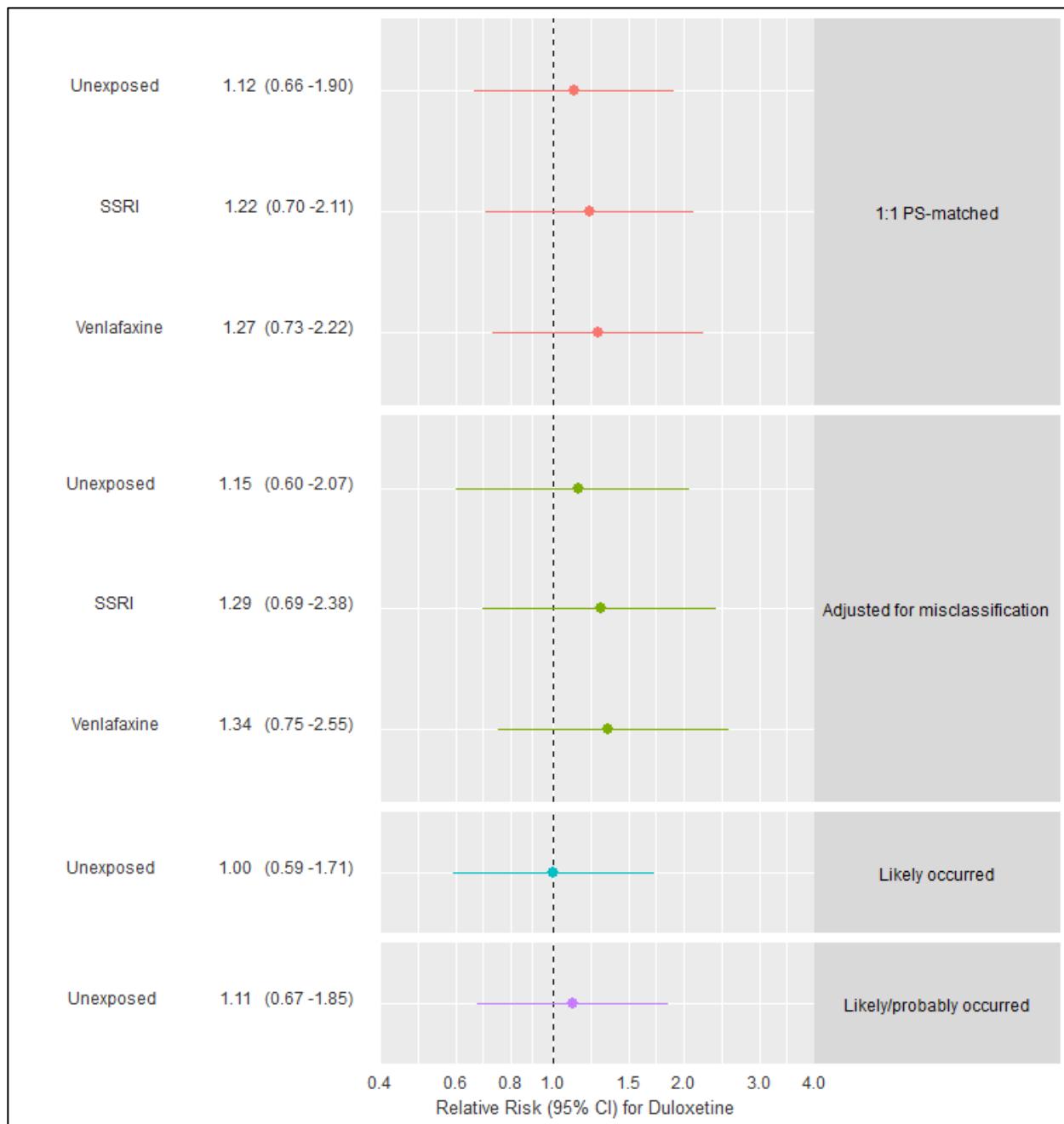


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

sFigure 18 Risk of postpartum hemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses



sFigure 19 Risk of postpartum hemorrhage associated with exposure to duloxetine during the final 30 days of pregnancy: sensitivity analyses to address outcome misclassification

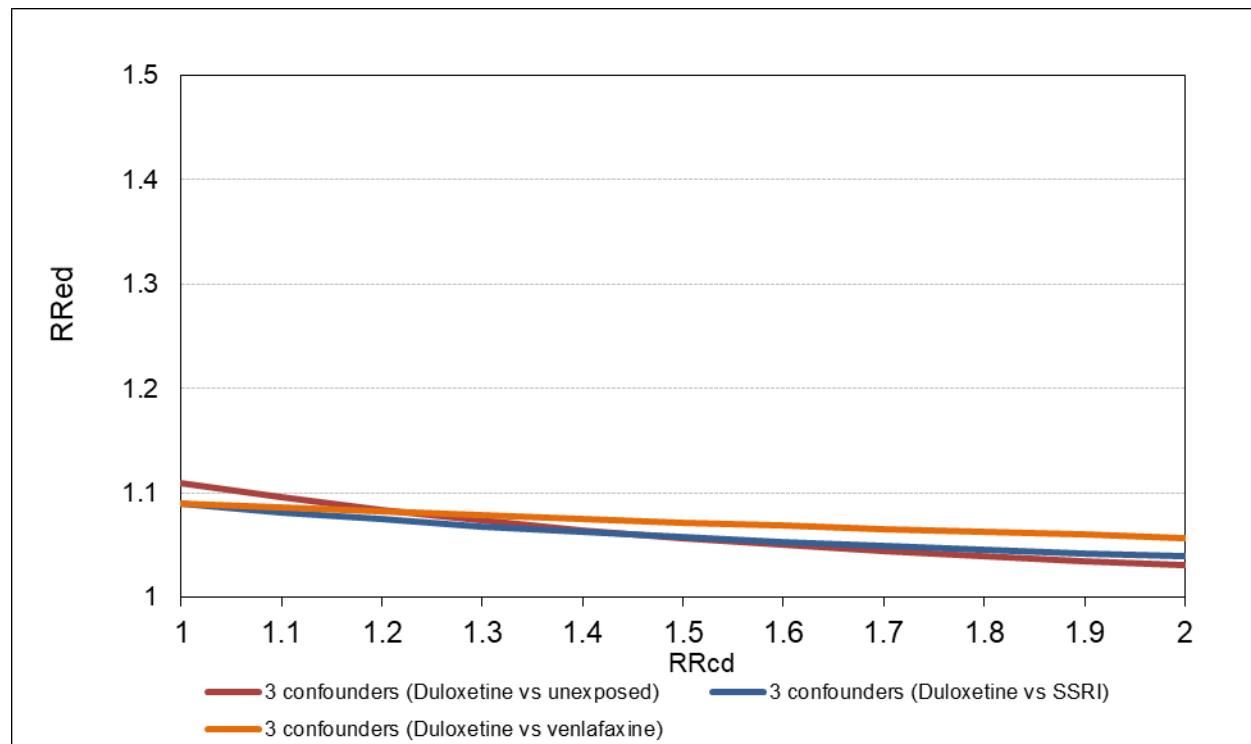


Note: Results from the probabilistic bias analysis based on the outcome validation study and the profile review should be compared against matched analyses.

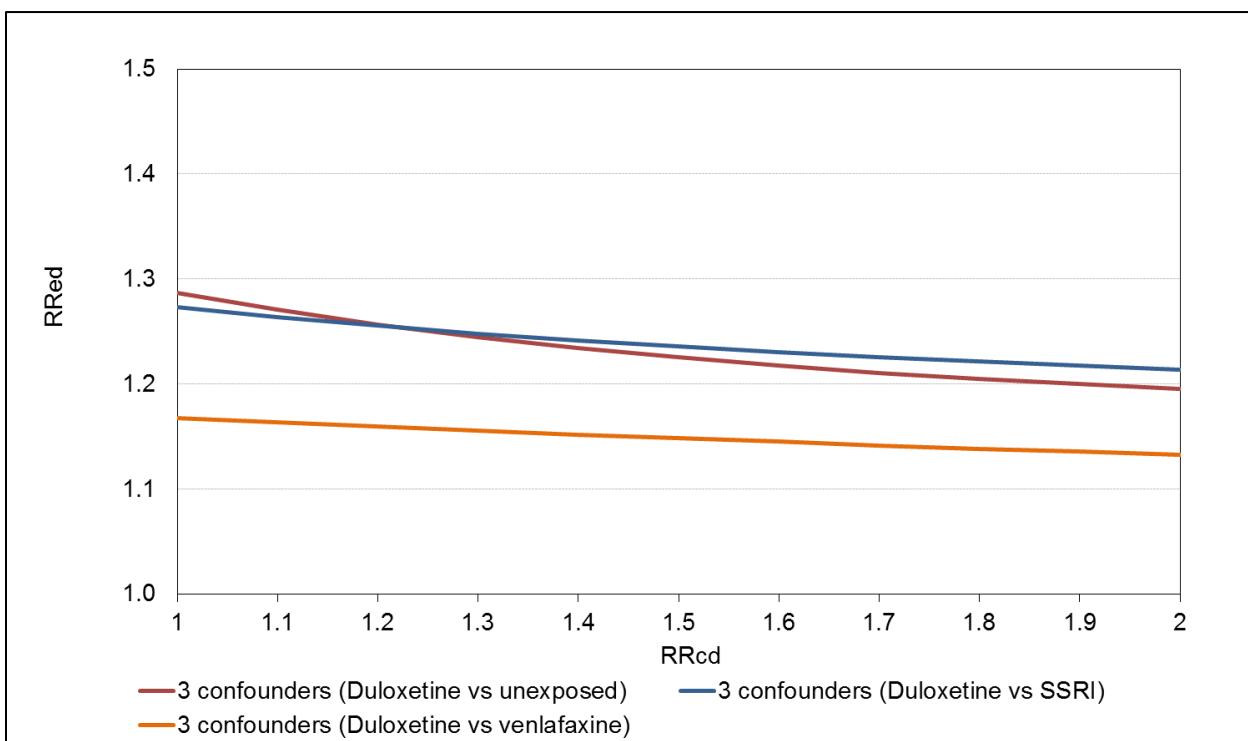
APPENDIX: EXTERNAL ADJUSTMENT OF THE RELATIVE RISK

There are covariates (e.g. smoking, obesity) that may be important confounders and that are not well documented in the source data but for which we can obtain supplementary information. In addition to adjusting for measured confounders by PS stratification, and for proxies of unmeasured factors by hPS stratification, we explored the impact of potential residual confounding by unmeasured lifestyle factors with additional information on covariates from external data using binary algebraic solutions, and/or bias analyses. We used publicly-available files from the National Health and Nutrition Examination Survey (NHANES) for 1999-2014, restricted the sample to women of childbearing age, stratified them based on insurance (Medicaid vs. private), and assessed the association between use of duloxetine and potential confounders (e.g., BMI, alcohol, and smoking). Information from the literature was used to inform estimates of the strength of the association between these factors and the outcome.

Figure 20 External adjustment of the observed relative risk for any malformation to account for confounding by obesity, smoking, and alcohol using NHANES

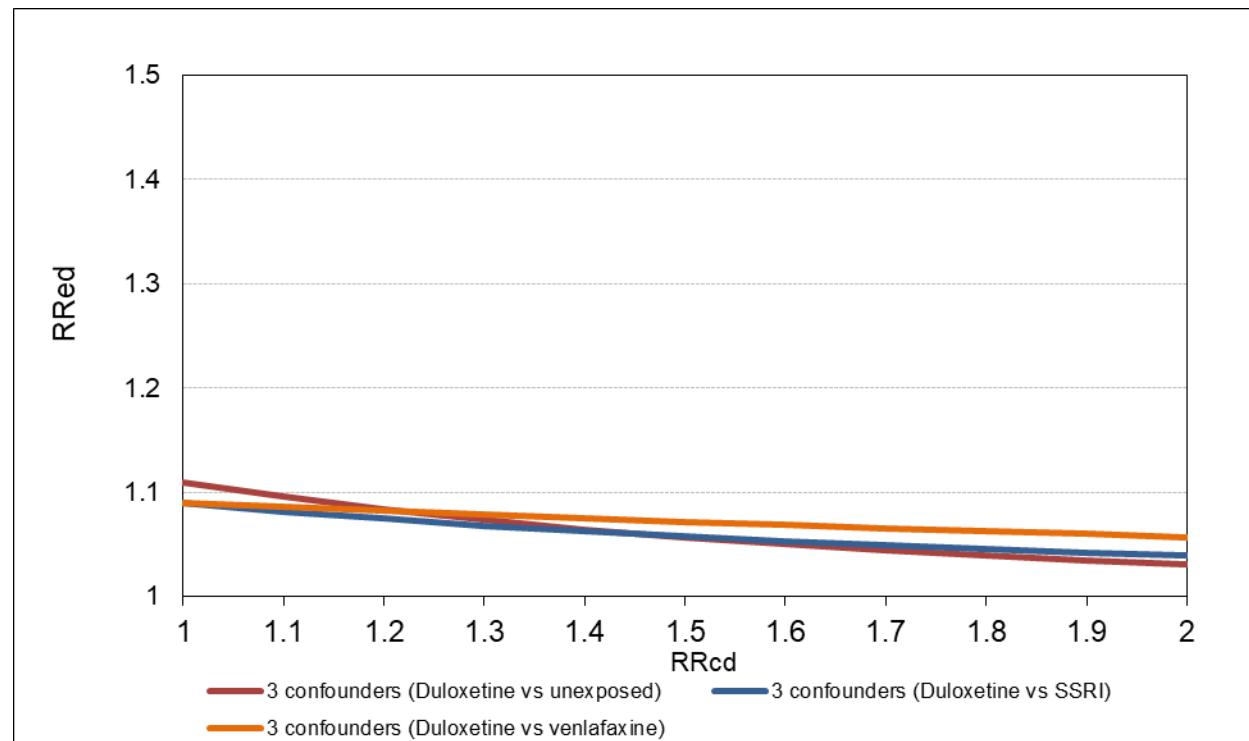


sFigure 21 External adjustment of the observed relative risk for cardiac malformations to account for confounding by obesity, smoking, and alcohol using NHANES

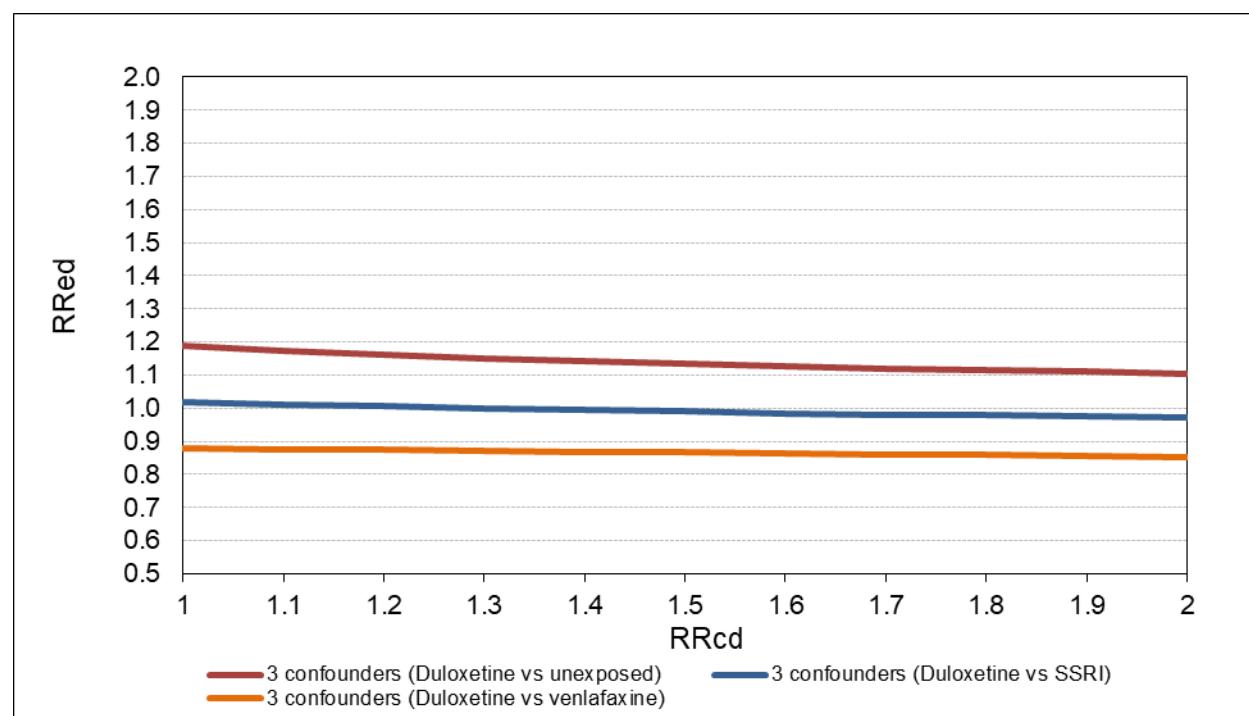


sFigure 22 External adjustment of the observed relative risk for preterm/SGA to account for confounding by obesity, smoking, and alcohol using NHANES

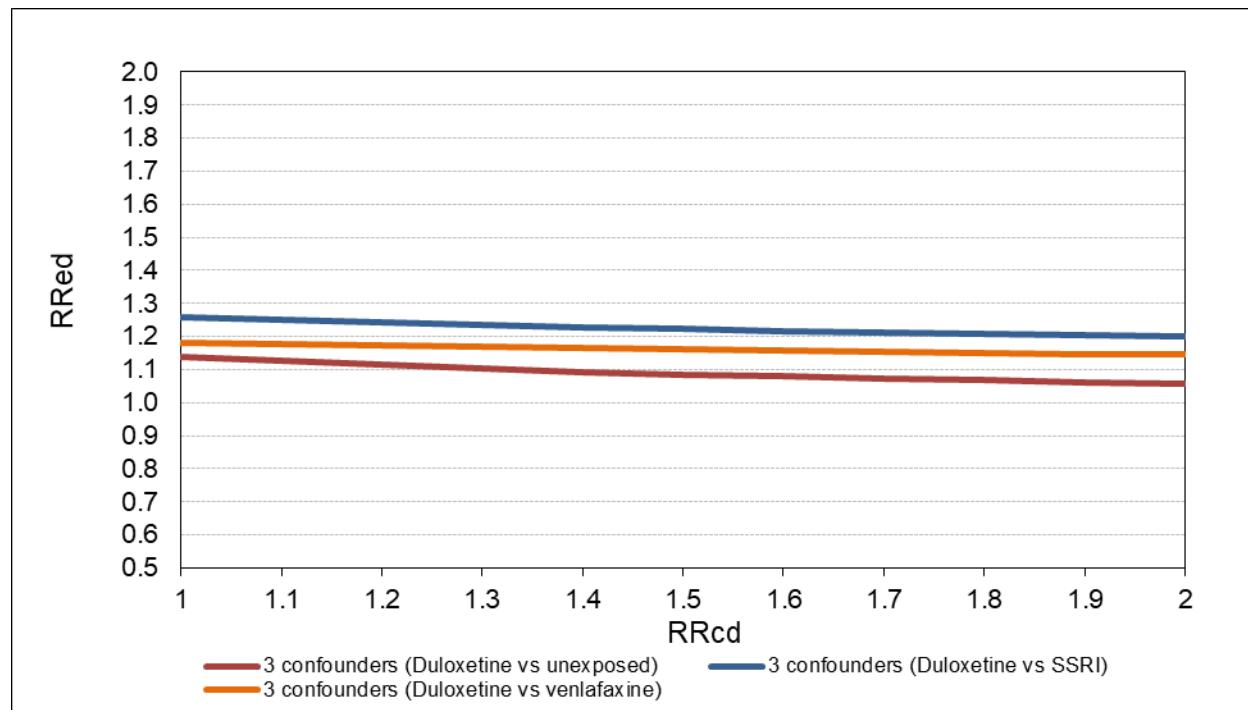
Outcome- Preterm (Early exposure period)



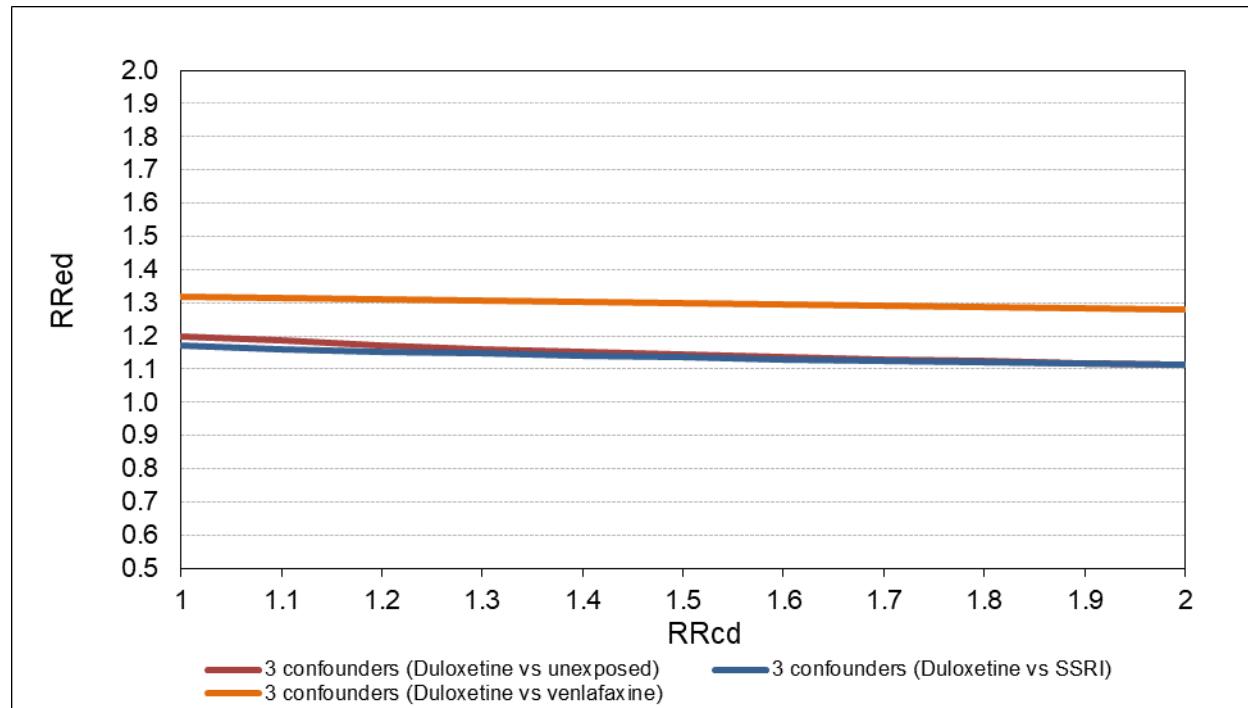
Outcome- Preterm (Late exposure period)



Outcome- SGA (Early exposure period)

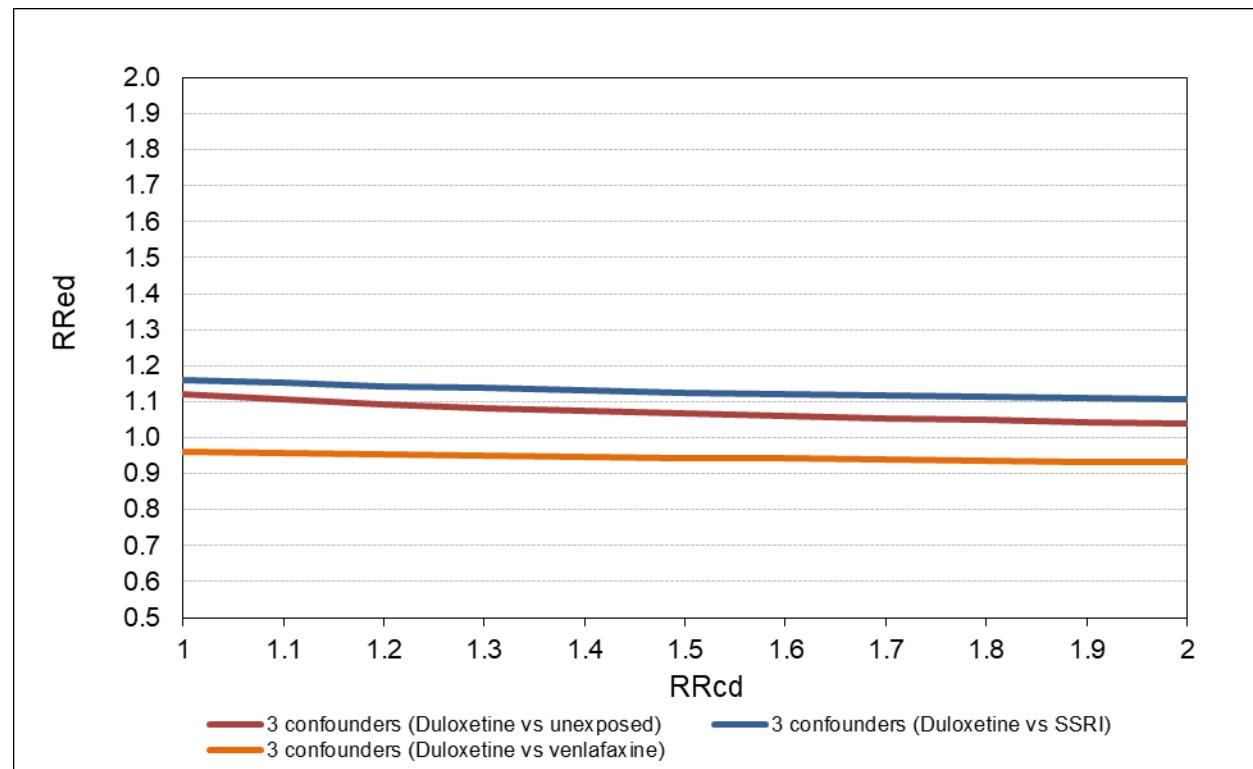


Outcome- SGA (Late exposure period)

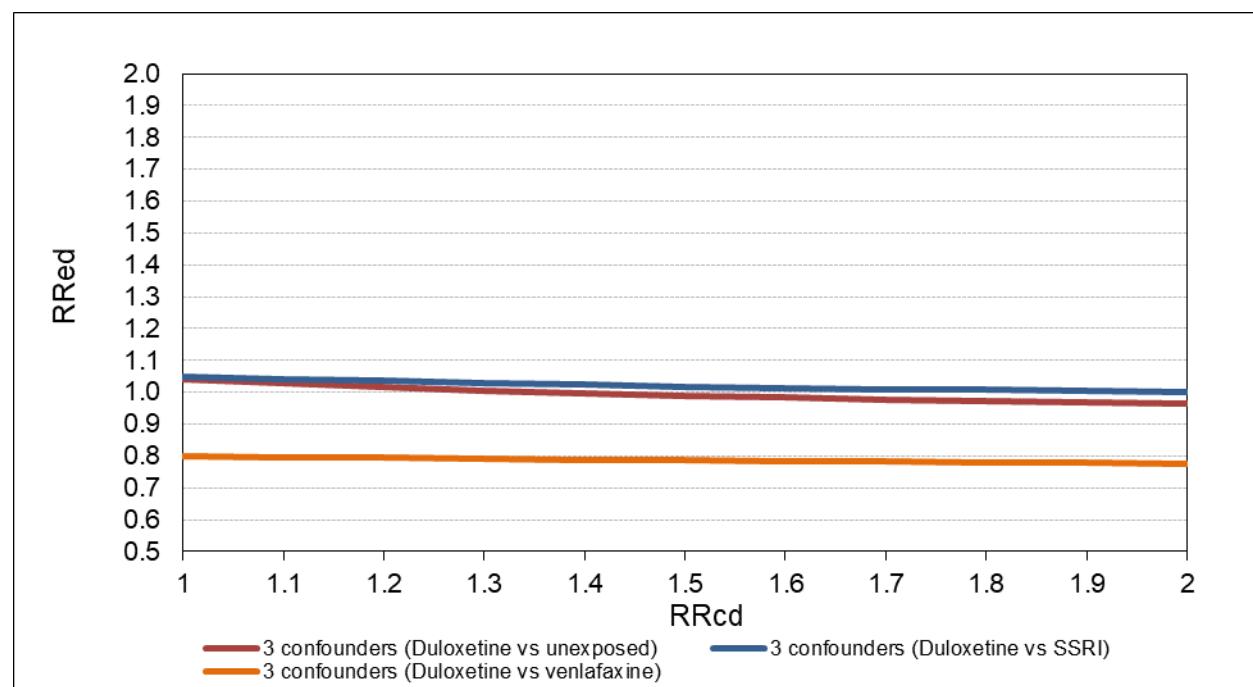


sFigure 23 External adjustment of the observed relative risk for preeclampsia to account for confounding by obesity, smoking, and alcohol using NHANES

Preeclampsia (Early exposure period)



Preeclampsia (Late exposure period)



sFigure 24 External adjustment of the observed relative risk for postpartum haemorrhage to account for confounding by obesity, smoking, and alcohol using NHANES

